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VOLUME XLII

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A CASE OF VACCINIFORM BLEPHARITIS DUE TO AN ATYPICAL HERPES VIRUS

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From the Department of Filterable Viruses, Johns Hopkins School of Hygiene and the Department of Ophthalmology, Johns Hopkins Medical School

The extent of the domain in which the herpes virus operates as a morbific agent has been the subject of much discussion during the twelve years that have elapsed since Grüter (1) discovered the infectious character of herpetic keratitis. Not only has the clinical concept of herpes been redefined, but such widely dissimilar diseases as epidemic encephalitis and sympathetic ophthalmia have been attributed to the same or to allied organisms. It may not, therefore, be without interest to report the isolation of a strain of herpes virus from a non-herpetic lesion.

REPORT OF CASE

The patient was a white girl, fourteen years of age whose family and past history revealed nothing of interest excepting the fact that she had been vaccinated in childhood with an excellent take (typical scar), and again without take, one year previous to this attack. No history was obtained of exposure to anyone affected with an eruption similar to that which she developed.

On October 16, 1926, she first noted an inflammation of the lids and conjunctiva of her left eye. There was very little pain but severe itching. When first seen on the fourth day of the affection, a vesicular and pustular eruption was apparent over the skin surfaces and margins of her left eyelids, together with a diffuse congestion of the conjunctiva. On the fifth day the left preauricular gland became enlarged and painful. On the sixth day most of the palpebral vesicles had become pustules, varying from 1 to 3 mm. in diameter. The larger ones were definitely umbilicated. A few small vesicles had made their appearance on the bulbar conjunctiva. The patient complained of no general discomfort. There was a temperature of 99.2°F., which rapidly subsided to normal. The general physical examination

was negative. The urine was normal. The blood count showed a moderate secondary anaemia. The white blood count and the differential count were normal.

Smears made from the pustules showed great numbers of lymphocytes, but very few polymorphonuclear leucocytes. No bacteria or cell inclusions were noted. A few colonies of staphylococcus albus were obtained on culture.

During the next two days the lesions increased in size, and many became confluent. The condition at this time is shown in the accompanying illustration (Fig. 1). A few scattered vesicles appeared on the right eyelid. From the eighth day onward the condition steadily

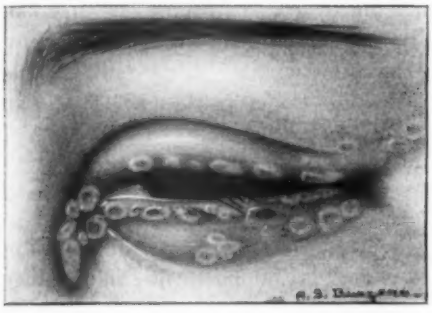

FIG. 1

improved. The swelling of the preauricular gland subsided. The conjunctival vesicles disappeared. The skin lesions became crusted and finally disappeared, leaving very fine pock-like scars. Three weeks after the onset the left submental gland became swollen and fluctuant. Under local anesthesia this was incised and drained; chocolate-colored pus was evacuated, from which a staphylococcus aureus was obtained on culture.

ANIMAL INOCULATION

On the sixth day of the illness, when the eruption was at its height, the skin over an unbroken vesicle, after being carefully cleansed with alcohol, was incised with a sterile knife and the fluid contents were

gently rubbed on the cornea of a rabbit which had been cocainized and lightly scarified with a sharp needle. Twenty-four hours later numerous tiny vesicles were seen along the line of scarification. As these grew in size a diffuse opacity of the cornea developed together with a profuse purulent secretion from the conjunctiva.

CORNEAL TRANSFER

Four days after the inoculation of the first rabbit, scrapings from its cornea were inoculated in the same way into a fresh rabbit's cornea and this process was then repeated, always at four-day intervals, through a series of eighteen passages in all of which the infection ran an essentially identical course. No rabbit developed symptoms of generalized herpetic infection after corneal inoculation and no lesions other than those described were observed. The corneal infection, however, was as severe as that produced by the most virulent strains of herpes virus with which we are familiar.

In some cases the passage was made from one eye to the other eye of the same rabbit. When this was done the reaction of the second eye was always much less severe than that of the first. It subsided much more rapidly and left no residual corneal opacity such as almost constantly resulted in the first infected eye.

MICROSCOPIC STUDY OF INFECTED CORNEAE

Eyeballs of animals of this series were enucleated 24, 48, and 72 hours after inoculation, fixed in sublimate alcohol and stained with haematoxylin and eosin. Sections showed that 24 hours after inoculation the corneal epithelium had become separated from Bowman's membrane in the region of the lines of scarification. Many of the nuclei of the epithelial cells were enlarged, and multinucleated cells were often seen. A few polymorphonuclear leucocytes were present in the substantia propria. After from 48 to 72 hours the purulent infiltration was much more intense and in some spots the epithelium was lacking. The most striking feature in the microscopic picture of the lesions was the presence of typical oxyphilic inclusion bodies within the swollen nuclei of the epithelial cells. Between these inclusions and the nuclear membrane was a clear zone, while upon the

membrane itself bead-like forms of chromatin were sometimes discernible. They were seen in all corneae sectioned, including those removed 72 hours after inoculation, and were also found in the cornea of the rabbit which had been inoculated directly from the patient.

INTRACRANIAL INOCULATION

Despite the high virulence which the virus showed on corneal inoculation, great difficulty was experienced in establishing an intracranial infection. Indeed, intracranial inoculation was successful only after the virus had been transferred from cornea to cornea in a long series of passages. The virus may therefore be quite properly characterized as unusually dermatrophic. The several failures and the finally successful intracranial transfer are enumerated in the table. The technique of intracranial inoculation was as follows. The infected cornea of a rabbit was anaesthetized with cocaine and the corneal epithelium scraped off with a sterile knife and suspended in salt solution. A fresh rabbit was then anaesthetized with ether, and after the skin just behind the outer canthus of one eye had been shaved and cleansed, a hypodermic needle was passed through the lower part of the fronto-parietal suture and about 0.2 cc. of the suspension or its Berkefeld filtrate was injected.

As will be seen in the table, a typical herpetic encephalitis was finally produced by intracranial inoculation in Rabbit 760. No difficulties were experienced in further intracranial passages from the brain of this animal, which was preserved in glycerine. This strain of the virus has now been passed by intracranial inoculation through four rabbits, and in each passage it produced typical encephalitic symptoms. Emulsions of the brains of the rabbits in this series have produced typical keratoconjunctivitides on corneal inoculation. Aerobic and anaerobic cultures of the brain material in deep bouillon tubes gave no evidence of bacterial growth.

Histological study of the brains of animals which had succumbed to intracranial inoculation showed perivascular round-cell infiltration and foci of small round cells within the gray matter. No inclusion bodies were found.

TABLE I

Showing corneal passages and attempts at intracraneal inoculations with the "F" virus

DATE	CORNEAL TRANSFER	RESULT	DATE	INTRACRANIAL INOCULATIONS	RESULTS AND COMMENTS
October 22	R. 719, right eye with contents of pustule	Typical herpetic keratitis			
October 26	R. 720, right eye	Typical herpetic keratitis			
October 30	R. 721, right eye	Typical herpetic keratitis	November 2	R. 722, from right eye of R. 721	Negative
November 2	R. 710, right eye	Typical herpetic keratitis			
November 6	R. 6, Right eye	Typical herpetic keratitis			
November 10	R. 728, right eye	Typical herpetic keratitis	November 12	R. 724, from right eye of R. 728	Negative
				R. 725, corneal control	Positive
November 14	R. 722, left eye	Typical herpetic keratitis			
November 18	R. 738, right eye	Typical herpetic keratitis			
November 22	R. 738, left eye	Typical herpetic keratitis	November 24	R. 737, from left eye of R. 738	R. 737 died November 26, but no passage from its brain was accomplished
			November 24	R. 739, corneal control	Positive
November 26	R. 748, right eye	Typical herpetic keratitis			
November 30	R. 736, right eye	Typical herpetic keratitis			
December 4	R. 740, right eye	Typical herpetic keratitis			
December 8	R. 752, right eye	Typical herpetic keratitis	December 10	R. 753, from right eye of R. 752	Negative
				R. 754, corneal control	Positive
December 12	R. 759, right eye	Typical herpetic keratitis			
December 16	R. 762, right eye	Typical herpetic keratitis			
December 20	R. 765, right eye	Typical herpetic keratitis			
December 24	R. 765, left eye	Typical herpetic keratitis	December 27	R. 760, from left eye of R. 765	Positive
				R. 761, corneal control	Positive

IMMUNOLOGICAL EXPERIMENTS

In order to establish the identity of the virus, which we shall now call the "F" virus, experiments were performed to discover whether animals which had recovered from a corneal infection with the "F" virus would subsequently exhibit any general immunity to the same virus and also to the herpes virus. For this purpose the well known "JB" strain of herpes virus isolated by Flexner and Amoss (2) was used, and also a strain isolated by direct intracranial inoculation in rabbits from a vesicle in a case of labial herpes. This latter is designated as the "A" strain.

It was found that rabbits that had recovered from corneal inoculation with the "F" virus were, two months later, immune to reinoculation either corneally or intracranially with the "F" virus, and that they were likewise immune to either corneal or intracranial inoculation with either the "JB" or the "A" strain of herpes virus. It may be concluded, therefore, that the "F" virus is a strain of herpes virus. The character of these immunological experiments is exhibited in the following protocol.

PROTOCOL

November 10, 1926. Rabbits 710 and 728 were inoculated corneally with the "F" virus and a typical keratoconjunctivitis subsequently developed.

January 12, 1927. Rabbits 710 and 773 each received an intracranial injection of 0.25 cc. of a 10 per cent emulsion of the "JB" virus. Rabbits 728 and 767 were injected intracranially with 0.25 cc. of a 10 per cent emulsion of the "A" strain. Rabbits 773 and 767 served as controls for rabbits 710 and 728, respectively.

January 17, 1927. Rabbits 773 and 767 showed typical symptoms of herpetic encephalitis including tremors, gnashing of teeth, salivation, etc.

January 18, 1927. Rabbits 773 and 767 died. Rabbits 710 and 728 remained free from symptoms and were alive three months following the experiment.

SUMMARY

A case is reported exhibiting a pustular eruption on the eyelids. The lesions consisted of vesicles and pustules upward of 3 mm. in diameter; many of the pustules were umbilicated. This picture in no way suggested herpetic infection and except for the history of previous vaccination would have been regarded as a typical example of accidental infection with vaccine virus.

From this case a virus was obtained which, when inoculated into rabbits, produced lesions and symptoms similar to those produced by the herpes virus. Animals surviving infection with this virus were immune to typical strains of herpes virus. This strain, however, exhibited a difference from other strains of herpes virus in that the intracranial infection of rabbits could be elicited only after a long series of corneal passages.

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THE HEART IN MUSHROOM POISONING

ALBERT S. HYMAN, M.D.

From the Cardiac Clinic of the Witkin Foundation

Mushroom poisoning as the result of eating *Amanita phalloides* fungi is not particularly uncommon in the United States; Ford (1) has estimated that from 12 to 15 deaths occur annually from this cause. Jordan (2) reported 22 deaths in ten days from mushrooms obtained in the vicinity of New York City; *Amanita muscaria* was identified as the group of fungi responsible.

Mushroom poisoning is, however, more common abroad; Morner (3) collected several hundred cases from the literature of the continent. The greatest number of cases and deaths have occurred in France (4), and the French literature (5) abounds with the various aspects of mushroom poisoning.

As a rule, attention has been focussed upon the rather severe and striking gastro-intestinal symptoms and the familiar picture of violent abdominal pain, nausea, vomiting, diarrhea, and cold clammy sweating has been described by many authors (6). The visual, central nervous system, and renal complications have also been studied in some detail both from a clinical (7) (8) and experimental (9) (10) point of view.

Concerning the cardiovascular system, however, the available literature reveals only the most obscure observations in regard to the heart and circulation in mushroom poisoning. Wieser (25), for example, speaks of a pulse scarcely perceptible to the touch in *Amanita phalloides* poisoning; Rosenau (11) states that the pulse is sometimes quickened and sometimes very slow and irregular. Murphy (12) described two patients seen by him as having no palpable pulse at the wrist, but whose heart beats were fast, weak, and very irregular.

An opportunity for a rather complete cardiovascular study of a case of mushroom poisoning was presented through the courtesy of Dr. A. B. M. of Syracuse, New York, who referred his patient to the Witkin Foundation for observation.

The patient, S. T., a man 37 years old with an excellent past history, was one of a party of four spending their vacation period in a camping trip through the Adirondack Mountains in New York State. On the morning of August 7, 1926, a quantity of mushrooms found growing at the bottom of a deep rocky glen were cooked and eaten. In about three hours all were complaining of violent abdominal pain, followed by nausea and vomiting; two of the men had diarrhea. Dr. M. who was staying at a near-by hotel was called and promptly instituted gastric lavage on all. Three of the patients, after a more or less stormy gastro-intestinal upset, made a rather complete recovery, but the fourth patient, Mr. S. T., failed to respond to treatment.

His chief complaint was an agonizing frontal headache, vertigo, and blinding flashes of *green* light. In about eight hours, the abdominal signs had entirely subsided, but the patient became somewhat stuporous and was aroused with difficulty. His pulse up to this time had been regular and of good volume with a rate of 86 per minute; his blood pressure was systolic 120 and diastolic 68 mm. At 8 p.m., about 10 hours after eating the mushrooms, the pulse became irregular but continued to be of good volume with a rate of 94. The irregularity gradually became more marked and the patient's general condition much worse the next morning when an elevation in the temperature to 101.4°F. was noted.

Upon consultation by telephone, I suggested the use of intravenous glucose solution according to the method of Steinbrinch and Münch (13) and by 4 p.m., about 30 hours after the ingestion of the mushrooms the patient had recovered sufficiently to be transported to New York City. A specimen of the mushrooms was obtained and upon examination gave the typical "silver spoon reaction" of Wiley (14).

The patient was seen August 9, 1926, forty-eight hours after the consumption of the mushrooms. He had entirely recovered from his symptoms, though somewhat weakened by his experience. His pulse, however, was still irregular. A complete cardiovascular study was made, a brief résumé of which follows:

The patient was at his theoretical normal weight for his age and height standard. Under the Dresler white light he showed a suggestion of cyanosis of his mucous membranes. After a moderate effort (Wolffe) test he did not become unusually dyspnoeic.

Physical examination. To percussion the superficial area of cardiac dullness was not increased. The heart sounds were clearly heard over the entire precordium; at the apex, the second sound was accentuated over the first. At the base, the second aortic was louder than the second pulmonic. All of the valve closures appeared to be synchronous and of fair total quality. The dominant rhythm of the heart, while regular, was interrupted frequently by a constant irregularity; the apical rate was about 60 beats per minute. All of the apical beats, including the irregular ones, were transmitted through to the radial artery; there was no pulse

deficit. No vagal effects could be elicited; the Refisch test was negative: the breath was held for a maximum of 58.4 seconds with no change in the pulse rate.

Arising in the mitral area was a soft blowing systolic murmur which had a short lateral transmission; the murmur was not changed after an effort test.

The lungs were essentially clear throughout; there were no râles at either base of the lungs posteriorly. Neither the liver nor the spleen was palpable; no free abdominal fluid was demonstrable. There was no edema of the lower extremities.

Blood pressure reactions. Oscillations were recorded from the brachial artery by the Pachon method as high as 180 and as low as 65 mm.; from the tibial arteries: 210/50 mm. The Vaquez ratio was about normal; the curve described was not characteristic.

Clinical blood pressure levels were established as systolic 135 and diastolic 75 mm.

Vital capacity estimations. The total volume of expired tidal air recumbent was 3300 cc.; standing 3600 cc. The Myers ratio was normal. Based upon his height of 65 inches this represented a reduction to 88 per cent, and based upon his weight of 140 pounds this is a reduction to about 86 per cent of his theoretical standard. These figures can be taken as suggesting a rather intact myocardial reserve.

Fluoroscopic examination revealed a rather pendulous heart with a tendency toward an aortic configuration. The movements and pulsations of the ventricles and large vessels were normal. On deep inspiration the pericardium stripped free from the diaphragm; no adhesions were noted. The diaphragmatic excursions were equal and of good amplitude. The lung fields were essentially clear except for a moderate hilar clouding.

Orthodiagraphic measurements showed the heart to be a bit widened in its diagonal diameter which measured 14.2 cm. The aortic arch measured 8.1 cm.

Eye-ground examination. The fundi of both eyes were readily visualized; no vascular or other changes were noted.

Laboratory data. Urine: slight trace of albumin, no casts. *Blood:* Hgb. 85 per cent. R.B.C. 4,800,000. W.B.C. 9,400 with 65 per cent polys.

The graphic records were of exceptional interest and are presented in detail as the main contribution of this paper. Simultaneous electrocardiographic and polygraphic tracings were made to demonstrate the relation between the electrodynamic phase of the cardiac cycle and the actual mechanical contraction of the left ventricle. An analysis of the tracings shows upright P-waves in all leads but of very low voltage. The P-R interval measures 0.20 seconds, the upper normal limit of conduction time (15). The QRS-complexes are dominantly upward in Lead I but downward in Lead III; the complex is delayed to 0.18 second (normal: 0.08) with a coarse arborization movement. The T-waves are di-phasic of the dextro-type; i.e., downward then up

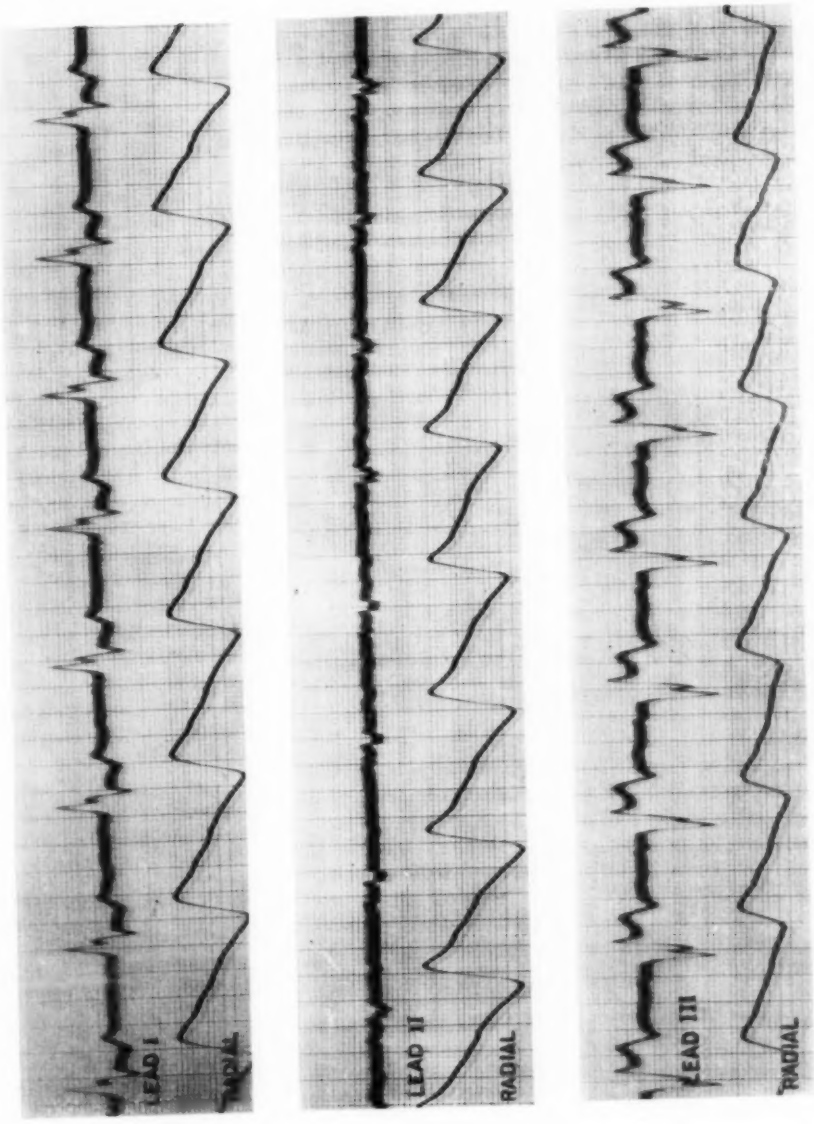

FIG. 1. RECORDS TAKEN AUGUST 9, 1926

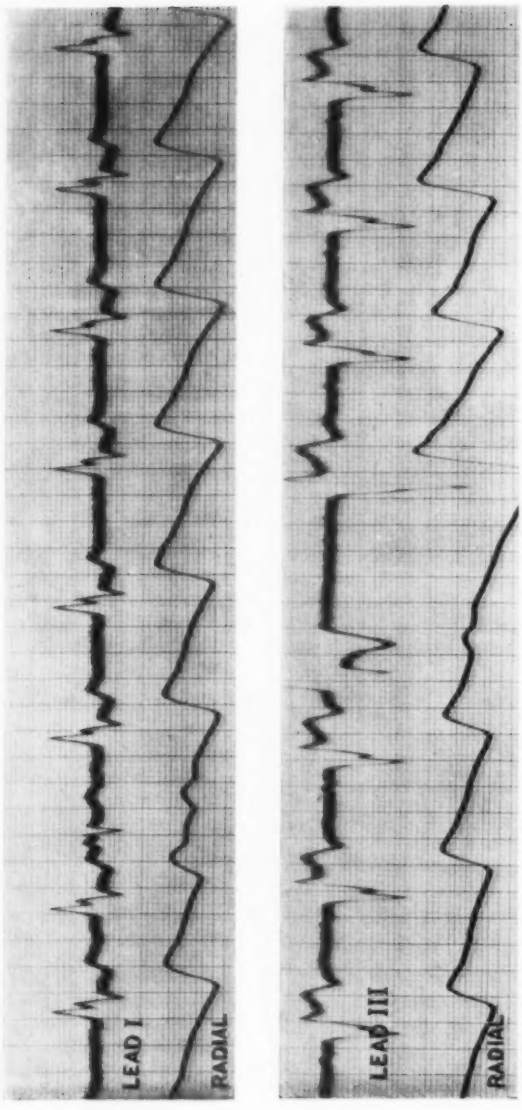

FIG. 2. RECORDS MADE AUGUST 9, 1926; THE IRREGULARITY OF THE PULSE IS SEEN TO BE DUE TO RIGHT VENTRICULAR EXTRASYSTOLES

in Lead I and upward then down in Lead III before the iso-electric line is reached. All of the waves in Lead II are of low voltage. There

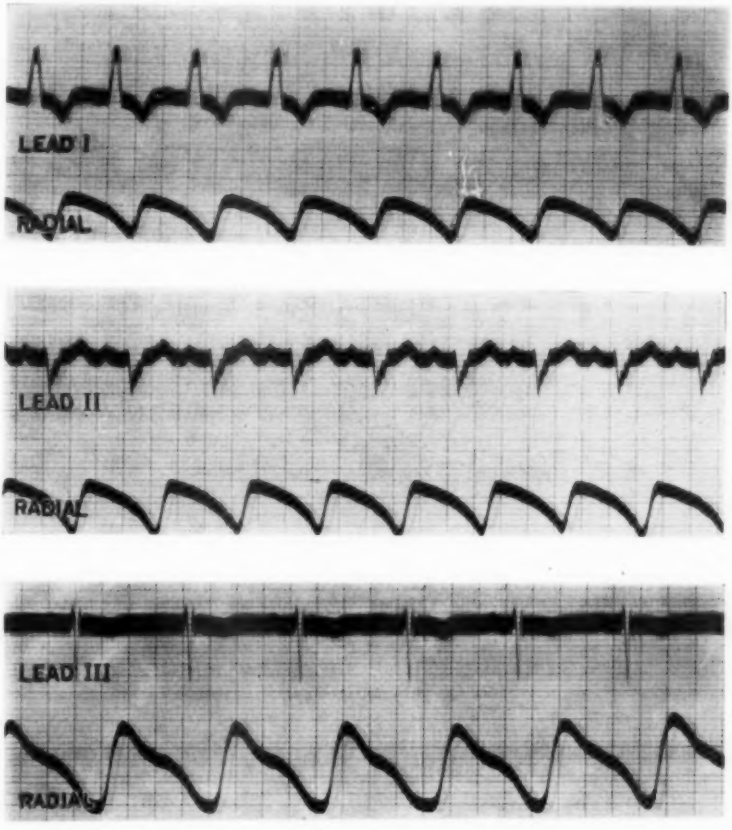

FIG. 3. RECORDS MADE AUGUST 25, 1926, 18 DAYS AFTER THE EATING OF THE MUSHROOMS

is a normal auriculo-ventricular rhythm with a rate of about 60 beats per minute.

Figure 2 shows the irregularity which is due to a well compensated extrasystole arising probably from an unstable ectopic focus in the

right ventricle. The premature beat occurs late enough in diastole to open the aortic valves and make itself felt as a smaller beat in the radial pulse.

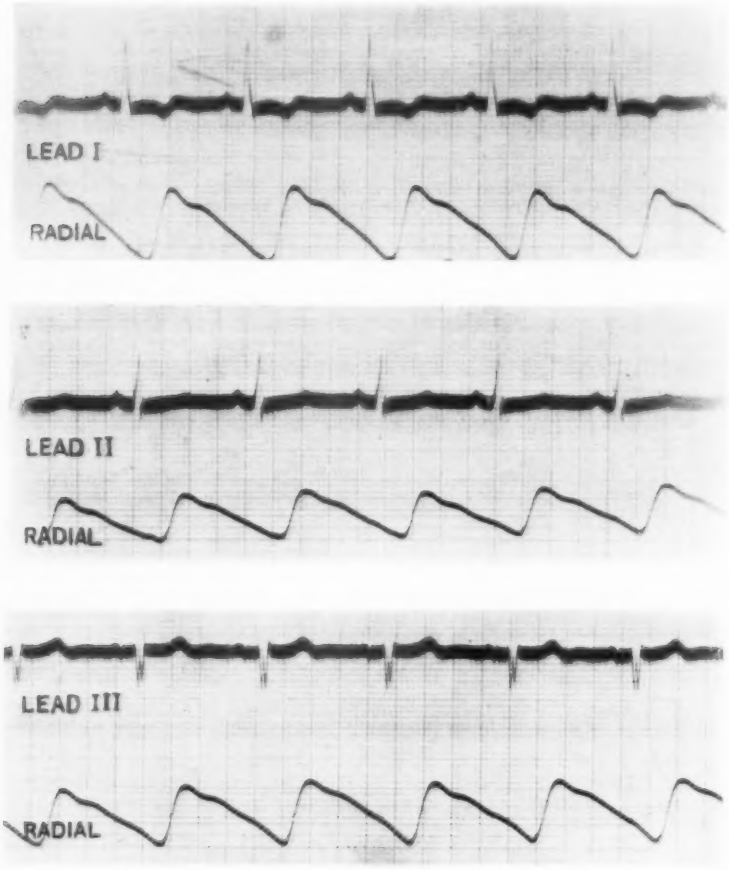

FIG. 4. RECORDS MADE DECEMBER 17, 1926; 4 MONTHS AFTER THE MUSHROOM POISONING

A tentative electrocardiographic diagnosis of a right main bundle branch block with extrasystoles of right ventricular origin was made.

After a few days' rest without special treatment the patient returned home and was seen again on August 25, eighteen days after the mush-

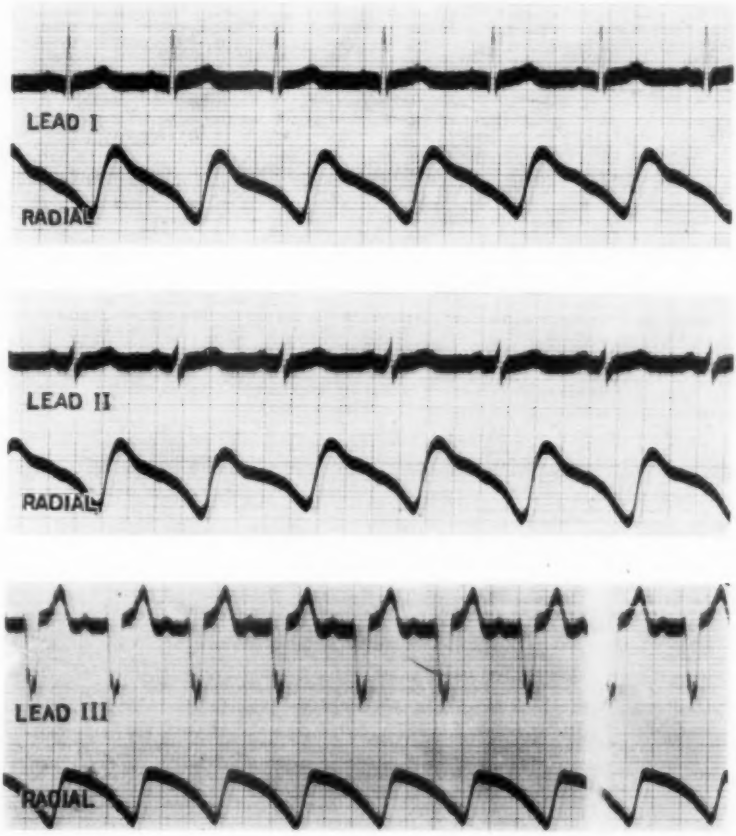

FIG. 5. RECORDS MADE MAY 14, 1927; 9 MONTHS AFTER THE MUSHROOM POISONING

room poisoning. He had no specific complaints and was preparing to return to his business.

A second graphic study was made; the evidence of severe myocar-

dial damage was still present, though perhaps not so marked as at the first examination. The QRS-complexes were now delayed to 0.14 second with a very fine arborization movement (See Lead III). T_1 was still inverted but no longer di-phasic; T_2 and T_3 were upright and well formed. All of the waves in Lead II were of increased voltage. The rate had increased to about 100 beats per minute.

The patient was not seen again until December 17, 1926, four months after the phalloides poisoning. He was enjoying good health. A third electrocardiographic and polygraphic study was made. The P-R interval now measured 0.16 second. The QRS-complexes had returned to a normal transmission time of 0.08 second; QRS_1 was upright and unarborized except for a suggestion of thickening in the base of the descending limb. QRS_3 was downward and had a coarse splitting. T_1 was still inverted, though perhaps less so than on the previous examinations. There was a normal A-V rhythm with a rate of 74. The patient's general physical examination remained practically unchanged.

In response to a follow-up letter, the patient graciously returned for a final examination on May 14, 1927, about nine months after his poisoning attack. The tracings now showed a moderate left axial rotation of the heart with no delay or splitting of the QRS-complexes. T_1 had become upright and well formed, while T_3 tended to be somewhat inverted. The rhythm was regular with a rate of 76. The patient complained of no symptoms referable to his cardiovascular system.

COMMENT

The discovery of the electrocardiographic changes found in this case without associated physical signs or symptoms of any serious moment is fruitful of much academic speculation. With graphic evidence of severe myocardial mischief, the rôle of the *amanita phalloides* poisoning is suggestive, yet the specific lesion requires considerable study.

Disturbances in the form and transmission time of the initial ventricular complex of the electrocardiogram have been called bundle-branch block, arborization block, and intraventricular block by various authors (16) (17) (18) (19).

In the form seen in Figures 1, 2, and 3, the lesion has usually been associated with disease involving the right branch of the His bundle. Such lesions, as a rule, would suggest a rather guarded prognosis because of the associated myocardial damage. Recently, however, Willius and Keith (20) have described three cases in which there was a recovery to normal after the finding of such bundle-branch damage.

A review of the pathological anatomy in *Amanita phalloides* and *muscaria* poisoning is interesting. Wieser (25) described two cases in which he found fatty degeneration of the muscle cells of the heart. Sahli (21) also discovered lipoid changes in the muscle fibers; Moers (21) reported finding hemorrhages into the myocardium and pericardium in 3 cases. Schurer (21) had an opportunity of making a post-mortem examination of a child's heart about thirty-five hours after the ingestion of *Amanita phalloides;* he found extensive fatty degeneration of the heart muscle. Finally, Miller (21) in 4 cases reported that the heart showed fragmentation and fatty deposition in the papillary muscles especially, and widespread infiltration in the myocardium.

Cushney (22) states that muscarine, probably the toxic substance of poisonous mushrooms, acts upon the mammalian heart by stimulating the myoneural junctions between the inhibitory fibers and the contractile substance of the heart, causing a slow and very irregular pulse.

In the case presented, one may assume, perhaps, that the phalloides poisoning was manifested by considerable myocardial damage in the region of the anterior papillary muscles of the right ventricle. Tandler (23) has shown the close anatomical relationship between the right division of the conducting system and the papillary muscles. This region may have been the focus of the ectopic beats seen in Figure 2. In this connection the cause of the T-wave inversion in the first lead is suggestive; I have previously shown a similar change in the case of a stab wound of the heart (24). In this latter case there were also right ventricular extrasystoles.

SUMMARY

1. A case of *Amanita phalloides* poisoning with cardiovascular symptoms has been studied by graphic and other methods.

2. Electrocardiographic examination revealed changes usually ascribed to right bundle-branch block.

3. An irregularity in the pulse was found to be due to right ventricular extrasystoles.

4. Post-mortem findings in such cases show extensive myocardial damage due apparently to a fatty degeneration of the muscle cells. The long period required for repair (about nine months) suggests the extent of the cardiac mischief.

5. The graphic evidence of extensive and widespread myocardial disease, while usually of ominous prognosis, does not always exclude complete recovery.

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THE AREA FRONTALIS OF THE CEREBRAL CORTEX OF THE CAT, ITS MINUTE STRUCTURE AND PHYSIOLOGICAL EVIDENCE OF ITS CONTROL OF THE POSTURAL REFLEX[1]

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INTRODUCTION

Work of investigators within the last few years has produced evidence that after removal of small portions of the cerebral cortex of the cat abnormalities in extensor tonus may, with appropriate methods, be demonstrated in the musculature of the extremities. These data are suggestive but by no means conclusive, nor can the data be entirely harmonized with other information derived from kindred observations. Since the phenomena reported must be bound up in some way with the regulation of the postural reflex, the subject of the physiological mechanism of this reflex and the possible morphological pathways involved must be introduced.

It was in 1896 that Sherrington first reported that after transection of the brain of a mammal (cat or dog) through the cephalic portion of the mesencephalon, a tonic contraction of the extensor musculature of the body ensued; the extremities were stiffly extended, the neck was extended or retracted and the tail dorsoflexed. He later pointed out that this extensor hyper-tonus was present in those muscles that normally counteract the force of gravity; the operation freed the antigravity muscles from some inhibitory control lying above this plane of the injury (1897–98). Sherrington referred to this tonic contraction of the extensor musculature of the body following transection of the brain-stem at a particular level (at the level of the superior colliculi) as decerebrate rigidity. A general summary of recent literature dealing with the control of the postural reflex by the central nervous system has been furnished by the present author in another place (Langworthy, 1927b).

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REVIEW OF LITERATURE

A. Extensor hyper-tonus after unilateral lesions of the brain

Sherrington further found that if one hemisphere was removed, the rigidity appeared chiefly on the same side on which the hemisphere was cut away. Some amount of extensor rigidity on the side opposite to the lesion was, however, not uncommon. The extensor rigidity was, however, inconstant and after initial development might subside and again reappear, and so on several times over.

Thiele (1905) also was able to produce unilateral rigidity after unilateral transection of the brain. If the cut was made forward in the region of the thalamus and anterior corpora quadrigemina marked contralateral rigidity appeared. When the lesion was further back in the region behind the anterior corpora quadrigemina, ipsilateral rigidity was obtained with only slight contralateral. These facts seemed to point to the conclusion that the inhibitory influence, which Thiele believed came not from the cerebral cortex but from the region of the thalamus, was a crossed one and that the decussation took place high up in the region of the rubro-spinal tract.

Weed (1914) endeavored to identify the inhibitory tract whose interruption caused the marked extensor hyper-tonus. The cut surface of the brain-stem in a decerebrate preparation was explored with an electric current; the area stimulated was that ordinarily exposed in the technique of decerebration. When the stigmatic electrode with a very weak current was applied to the mesial fraction of the cerebral peduncles with an insulator in the mid-line to prevent spread of current, it was found that the extensor rigidity entirely disappeared in the ipsilateral limbs and was diminished in the contralateral. The inhibitory pathway outlined by Weed appeared to arise in the cerebral cortex, the fibers forming the fronto-ponto-cerebellar tract. Cobb, Bailey, and Holtz (1917) later confirmed the observation of Weed that stimulation of the mesial portion of the cerebral crura inhibited the rigidity.

Bazett and Penfield (1922) decerebrated cats with sterile technique and kept them alive for a number of days by carefully controlling the temperature in a water-bath or warm box; they also prepared in like manner a number of hemi-decerebrate preparations. In these latter

animals, after all stimulation effect has passed off, the control is removed from some structure whose unantagonized action produces tonic extensor rigidity in the contralateral limbs and tonic flexor rigidity in the ipsilateral.

Magnus and Rademaker (1924) are of the opinion that centers in the cerebral cortex and thalamus have no part in the control of the postural reflex. They reported that the thalamus animal preserved normal tone in the muscles and could coördinate its movements. It was consequently able to stand, sit, walk, jump and if it fell from a height could regain its normal posture immediately. The tonus was in fact unaltered and the righting-reflexes intact, after transection through a plane extending from the anterior part of the anterior corpora quadrigemina to the pes pedunculi, 2 mm. oral to the emergence of the oculomotor nerve and just cephalic to or through the oral ends of the red nuclei. Rigidity developed after transection through the plane of the posterior part of the anterior colliculus to the peduncles caudal to the emergence of the third nerve. This section passed through or behind the caudal end of the red nucleus.

B. Extensor hyper-tonus after injury of the cerebral cortex in cats

Investigations touching more intimately the present problem began with the work of Warner and Olmsted (1923). The experiments were acute and in every case terminated within twenty-four hours. Contralateral extensor rigidity of fore- and hind-legs followed the ablation of one whole cerebral cortex anterior to the thalamus; this rigidity was interrupted by walking movements. The extremities of the ipsilateral side also showed a slight increase in tone. If the electrically responsive motor area of the cerebral cortex of the cat was cut away, no increase in extensor tonus was present. But if the cortex anterior to this area was also removed, definite hyper-tonus developed in the contralateral fore- and hind-legs and this was seen even if the remainder of the motor area was intact. The rigidity, often masked by progressive movements, was clearly demonstrated under anesthesia deep enough to abolish these movements.

These experiments were extended by Olmsted and Logan (1925) with observations upon chronic preparations prepared with aseptic technique. In localizing the lesions of the cortex they used the

nomenclature of the Winkler and Potter atlas (1914). Winkler and Potter place the motor area in the anterior and posterior sigmoid gyri surrounding the sulcus cruciatus; the anterior sigmoid gyrus is continuous mesially with the gyrus proreus which forms the anterior pole of the hemisphere. These designations were scarcely definite enough to localize the small areas removed, even though photographs of many of the brains were shown. Olmsted and Logan divided their observations into groups according to the position and extent of the cortical injury. The control cats were operated upon in the usual way and the cortex was injured posterior to the motor area; no abnormalities of motility or of tone were observed.

In several cats the entire area around the sulcus cruciatus on one side (electrically responsive motor area) was destroyed; the contralateral legs were paralyzed but by the fourth day the cats were able to walk in a fairly normal manner.

In five cats the area frontalis was removed on both sides; only one animal lived more than a week. All were restless after the operation and walking was continuous. When it was evident that they were trying to sit or lie down the hind-legs would become maximally extended. On suspending them, they showed as great extensor tone as decerebrate preparations.

Similar experiments were recently reported by King (1927) and a further study of these animals with additional histological and physiological data forms the subject of this paper. In King's experiments the electrically responsive area was carefully delimited, the areas removed were precisely located and the preparations were kept alive over a longer period of time than those reported by Olmsted and Logan.

C. Location of the area frontalis

It seems strange, considering the numerous studies of cerebral localization based upon experimental operative injuries, that this abnormal extensor tonus following removal of the area frontalis had not been reported previous to the study of Warner and Olmsted. For this reason the earlier observations concerning the function of this area and of the frontal lobes of mammals including man will be reviewed.

First, it is important to delimit accurately that portion of the frontal lobe with which this paper is particularly concerned. Brodmann (1909) described a distinct histological area found just anterior to the electrically responsive cortex of all mammals. This area was characterized by well developed strata of supragranular and infragranular pyramidal cells, by a wide molecular layer and an extremely rudimentary granular layer. Brodmann called it the area frontalis agranularis. He found in his comparative studies that it was poorly developed in lower mammals where it tended to be intermingled with the electrically responsive motor cortex.

Campbell (1905) had previously identified a structurally similar area in the cerebral cortices of Primates including man. It lay anterior to the electrically responsive motor area; in fact the transition between these two areas was a very gradual one. Previous physiological experiments of Grünbaum and Sherrington (1901) upon the same monkeys whose cortices were examined histologically by Campbell had proved this intermediate area was non-responsive to electrical stimulation. These workers demonstrated that the anterior extent of the responsive area was less than the results of previous investigators tended to show.

Campbell proved that the intermediate precentral area bears a strong histological likeness to the motor cortex; it embraces the classical area of Broca and may control the execution of skilled movements. There is no diminution in cortical depth from the motor area but the radiary zone is less pronounced. The small pyramidal cells are a little less closely packed, suggesting a numerical increase; the medium-sized pyramidal layer shows no distinctive points except an apparent increase in depth. The large pyramidal-cell layer forms a reliable guide to distinguish this region from the more anteriorly placed frontal convolution, for the cells show a surprising equality in size. The stellate layer is a narrow zone poorly supplied with cells, encroached upon by the pyramidal layers above and below. The large pyramidal cells do not approach the Betz cells in size and are even smaller than the other pyramidal cells; they show great uniformity in size. The polymorphic layer has no distinctive character.

In man the extent of this intermediate precentral area varies greatly in individual specimens, according to Campbell. On the mesial

surface of the hemisphere it reaches a great breadth; its lower border is the calloso-marginal fissure. On the upper surface of the hemisphere it is again extensive, reaching well forward on the superior frontal gyrus. At the lower level of the superior frontal gyrus it narrows and becomes confined to the anterior half of the ascending frontal and anterior central and to a small portion of the base of the middle frontal gyrus. It then sweeps forward covering most of the inferior frontal gyrus including some of the pars basilaris and the whole of the pars triangularis.

Hughlings Jackson (1895) believed that movements were represented at three levels of the central nervous system. The simplest movements are controlled by the cord, medulla and pons; the second level is the so-called motor area of the cerebral cortex, while the third or highest center is composed of centers occupying the frontal lobes, representing the more complex movements. Campbell hypothesized that the intermediate region represented this third level and that this particular stretch of cortex was especially designed for the execution of complex movements of an associative kind, *i.e.*, skilled movements in which consciousness and volition play an important part.

D. The area frontalis as the origin of the fronto-pontine tract

The connections existing between the area frontalis and subcortical centers have always been a matter of controversy and still offer a field for further investigation. Campbell (1905) thought that cells in this area gave rise to the fronto-pontine tract, and there is certainly some evidence for this hypothesis.

Flechsig (1876) early showed that in man the fibers of this tract became myelinated later than those of the cortico-spinal pathway. He maintained that these fibers were centrifugal as regards the cortex, having their origin in large pyramidal cells situated in the posterior portion of the three tiers of frontal convolutions. The fibers in man occupy the frontal portion of the internal capsule and terminate in the pons. Winkler and Potter (1914) describe a similar tract in the cat occupying the mesial portion of the cerebral peduncles.

Von Monakow's clinical case (reported by Nothnagel, 1897) showed, after extensive destruction of the cortex of contiguous portions of the second and third frontal convolutions, almost complete destruction

of the mesial segments of the crus. In this case there was also extensive destruction of subcortical tissue which complicated the question of origin of the fibers.

Ferrier and Turner (1898) reported, following ablation of the frontal lobe in the monkey, degeneration in the anterior segment of the internal capsule, in the most mesial and ventral parts immediately above the anterior commissure, in the medial tract of the crus and the corresponding portions of the pons; below this point the degeneration disappeared.

Dejerine (1901) believed that the fibers of the fronto-pontine tract arose in the cortex of the frontal and Rolandic operculum, but suggested that some of the fibers might come from the orbital surface of the third frontal convolution. He based his conclusions upon the study of degenerations following extensive lesions.

Mellus' (1907) experiments seemed to show that the mesial segment of the crus did not contain any cortico-pontine fibers coming by way of the anterior segment of the internal capsule. In a series of experimental ablations of small areas of cortex in the frontal operculum of the monkey he never observed any degeneration in the mesial segment of the crus.

Later von Monakow (1905) stated that through the anterior portion of the internal capsule there pass fibers coming from the first and second frontal convolutions and leading directly to the cerebral peduncle where they form a part of the mesial tract. Other analogous fibers proceed to the pons as fronto-pontine fibers.

Marinesco (1898) reported that as a result of partial or complete destruction of the frontal lobe in dogs and apes he could trace fine degenerated bundles of fibers into the corpus striatum, most clearly into the caudate nucleus.

Minkowski (1924) demonstrated pre-Rolandic fibers detaching themselves from the dorsal part of the lenticulo-caudate segment of the internal capsule and passing into the dorsal part of the head of the caudate nucleus. Here they pursued a dorso-median direction, meanwhile entering into contact with the cells of the caudate nucleus as they follow a course of some length. He also found them in the cat after ablation of the motor sigmoid cortex.

E. Reputed function of the frontal cortex

Many attempts have been made to associate the frontal lobe with the highest associative functions of the brain; observations in this field have been summarized recently by Bianchi (1922), a strong adherent of the theory. This work, vigorously attacked and defended, has been based largely on ablation experiments with little morphological control. Moreover, most of the important experiments have been performed upon monkeys where it is extremely difficult to extract the data bearing on the present work. For the pre-frontal area is the portion of the cortex most frequently removed, and it is usually impossible to judge as to how much of the intermediate precentral area, the subject of the present investigation, has been damaged.

From a study of war injuries Marie and Behague (1919) and Marie, Boultier and Bogaert (1924) have been able to associate a very definite clinical syndrome with injury of the pre-frontal region. This syndrome consists of hyper-excitation with a certain degree of childishness, euphoria with phases of depression, profound apathy and immorality with sexual perversion. The most important symptom is. disorientation in space without objective signs of vestibular injury. There is also a loss of very fine discrimination of primary characteristics of volume, quality and consistence. Similar cases were reported by Mott (1907) and Goldstein (1923). The findings in war cases have been summarized by Horrax (1921).

Dandy (1925), in order to facilitate the removal of a deep-seated brain tumor, reported an extensive resection of the left frontal lobe without any appreciable impairment. There was neither aphasia nor any contralateral motor weakness. In this operation the intermediate motor area was apparently not injured.

In mammals such as the cat and dog the difficulty of distinguishing pre-frontal from intermediate pre-central cortex is not present; for whereas the area frontalis finds its histological counterpart here, the pre-frontal area is extremely rudimentary. Italian investigators, forming their conclusions from ablation experiments upon these animals, maintain that the area frontalis has an essential inhibitory function.

In the present experiments it was necessary to locate accurately in

the cerebral cortex of the cat the areas to be removed. Previous physiological investigation in this laboratory (Weed and Langworthy, 1926) had delimited the electrically-responsive motor cortex surrounding the cruciate gyrus. The brains of these experimental animals were preserved and the motor cortex studied histologically. The findings in these latter experiments confirmed the extent of the motor cortex as determined by electrical stimulation (Langworthy, 1927). The physiological experiments were repeated at the beginning of the present study.

An accurate designation for the intermediate motor area is difficult to determine. Brodmann (1909) in his histological studies referred to the area frontalis agranularis. But a serious objection to this term may be raised. For granular or stellate cells are undoubtedly present, although few and inconspicuous, not forming a well defined layer. Moreover, Bolton (1914) and Watson (1907) have pointed out that it is important to distinguish a granular layer in all portions of the cortex. For this layer differentiates early both phylogenetically and embryologically. Projection fibers, afferent to the cortex, appear to terminate around these granular cells.

Campbell (1905) from his study of the human cortex separated out the intermediate pre-central area. The term intermediate is apt, since the structure of the electrically responsive motor cortex gradually changes anteriorly into that characteristic of this region. But the term pre-central can hardly be applied to the cat unless the sulcus cruciatus is considered homologous to the central fissure of Rolando. At the present time it is unwise to draw such an analogy. It is therefore proposed to speak in this paper of the intermediate motor area or area frontalis, distinct from the pre-frontal area which has attained such great development in Primates, particularly in man.

METHOD OF INVESTIGATION

A. Physiological

As a control to the ablation experiments and to map out accurately the areas to be removed, the electrically responsive motor cortex of the cat was carefully explored with unipolar stimuli in the manner previously described (Weed and Langworthy, 1926). Under ether

anesthesia, the skin, fascia, facial and temporal muscles were reflected and the bony cranium over the motor area removed widely with trephine and rongeurs. The dura was then cut away with sharp scissors and the exposed cortex dried with cotton pledgets. The unipolar method of stimulation was used; the indifferent electrode was fastened to the body; the stigmatic electrode was a platinum point mounted on a delicate spring. The animal was kept under light but adequate ether anesthesia during this period in order that voluntary movements might not be confused with cortical irritability.

No sterile technique was followed in the ablation experiments in which the preparations were observed only for one day. After the area to be removed had been positively identified, it was cut away with a sharp knife. Warm saline solution applied on cotton pledgets in most cases stopped the bleeding almost immediately. After the bleeding had ceased, the skin was approximated and the ether discontinued. The animals were studied after they had completely recovered from the effects of the anesthetic and were killed before the end of twenty-four hours.

Two approaches to the motor cortex were found useful in the animals prepared with aseptic technique for chronic preparations. If portions of the electrically responsive cortex were to be removed, the trephine opening was made in the temporal fossa. The temporal muscle was in this case found very useful for closure, the more so since in the cat it is difficult to effect adequate approximation of the dura and periosteum. In fact no attempt at suturing the dura was made; at the end of the operation it was carefully laid over the wound.

When the area frontalis was to be removed alone, it was necessary in all cases to open the frontal sinus. An operation was therefore devised whereby a trephine opening was made directly over this area. After the sinus had been laid open widely, it was thoroughly washed out with a 2 per cent solution of mercurochrome, "220." With small rongeurs the thin plate of bone separating the sinus from the cranial cavity was chipped away to the mid-line and to the floor of the sinus, exposing clearly to view the area frontalis. This exposure was extremely satisfactory and could be accomplished with very little trauma and bleeding particularly if young adult animals were used. When the operation was bilateral, the roof of the sinus was removed

across the mid-line. The opening in the cranial cavity was then made bilaterally, leaving a mesial ridge of bone in the posterior wall of the sinus.

Closure in this operation was more difficult. After the edges of the bone had been carefully smoothed off, the superficial and deep fascia was carefully approximated with interrupted stitches and the skin then closed. The closure was satisfactory since no cerebrospinal leak ever occurred. A serious objection to this operation would seem to be the danger of infection spreading from the frontal sinus. But infection never followed the procedure in this series of cases. In these experiments the cortex to be removed was cut away with a sharp knife or with a cautery. The knife injury was better localized; the cautery ablation was followed by less bleeding.

In another group of cats to be discussed in this paper, the pyramidal tracts were cut at the place where they decussate in the mid-line in the lower portion of the medulla. To gain adequate exposure for this operation an incision was made through the skin in the dorsal mid-line in the region of the occiput and upper cervical region. The neck muscles were carefully separated until the occipito-atlantoid ligament was clearly exposed. The cat's head was then maximally flexed and this ligament was cut in the mid-line with dural hook and fine scissors. In order for the operation to be successful, there must be no bleeding up to this point. After the brain stem is clearly exposed the mid-line must be accurately located; a head-light is almost essential for this part of the operation. A heavy straight needle used for suturing the skin was then inserted in the mid-line and drawn along until the brain-stem was cut sagittally from just above the lower border of the fourth ventricle through the first cervical segment. After this incision had been made, the extreme flexion of the head was relaxed and the bleeding controlled with cotton pledgets moistened with warm saline. Some of the animals stopped breathing for a short time after the operation. In these cases artificial respiration was performed till they recovered.

The behavior of a number of cats in whom the pontine fibers were cut in the mid-line at the point of decussation will also be mentioned; it is planned to describe these preparations in greater detail at a subsequent time. The brain-stem was exposed from the ventral

surface through the mouth somewhat after the manner described by Pollack and Davis (1923). The animal was placed on its back and the mouth held open with an appropriate apparatus. The soft palate was cut in the mid-line and pulled to the side, thus exposing clearly the roof of the pharynx. An incision was made through the mucous membrane and periosteum in the mid-line, and these structures were pulled to the side. The bone was then removed with a bone chisel and small rongeurs until the pons was clearly exposed. Bleeding was controlled by the use of bone wax. The dura was then opened with a hook and fine scissors and the pontine fibers cut in the mid-line. These animals were kept alive for one or two days as acute preparations.

Intra-tracheal anesthesia was given in all these operations. After the cat was relaxed under ether a small rubber catheter was inserted in the trachea. Compressed air saturated to the necessary degree with ether was then administered at low pressure (10 mm. Hg). The incisions were sealed with celloidin in the early operations, but this caused such a drawing of the skin that healing was retarded. Later it was found that if the skin was carefully approximated no protective covering was required. The post-operative care of the animals was also simple. In the few cases where shock and prostration were severe, tube-feeding for a day or two was sufficient to improve the condition of the animals. Most of the subjects were able to drink milk on the day following the operation. The animals were sacrificed at periods varying from three weeks to three months and the brains and spinal cords preserved in 10 per cent formalin.

B. Histological

The minute structure and extent of the area frontalis in adult cats and the maturation of this area in young kittens have already been described as seen in sections prepared for study of the structure and development of the cat's motor cortex (Langworthy, 1927). This series of sections has been enlarged and supplemented for the present needs. The cerebral cortices were fixed in 10 per cent formalin. Blocks were cut from the cortical tissue surrounding the sulcus cruciatus corresponding to the small areas outlined in Figure 1. At the same time longitudinal sections of the anterior and posterior sig-

moid gyri and transverse sections across the sulcus cruciatus were made to give a more general view of the relations of this whole region. The blocks were imbedded in paraffin, cut 10 micra thick and stained with thionin, iron hematoxylin and Ehrlich's hematoxylin and eosin.

The time of myelinization of the cortico-spinal and cortico-pontine fibers in the cat will be discussed. These sections of the brain-stem and cord of new-born and young kittens were mordanted and stained by the Weigert-Pal technique. A survey of this material in relation to another problem will also be found in an earlier publication (Langworthy, 1926).

The fibers degenerated after the cortical ablation experiments reported here were followed in sections stained by the Marchi and Weigert methods. Animals were sacrificed at the end of three weeks to provide Marchi material: the animals that lived three months or longer were used for the Weigert preparations.

EXPERIMENTAL OBSERVATIONS

A. Physiological

Under this heading both acute and chronic experiments will be reported. The acute experiments may be grouped under two headings, delimitation of the electrically responsive motor area and removal of portions of the cerebral cortex from this area and from the area frontalis. The chronic experiments have to do with cortical injuries in these same areas, also preparations in which the cortico-spinal tracts were severed without any injury to the cortico-pontine fibers, and those in which the cortico-pontine fibers were cut without injury to the cortico-spinal.

1. Electrical stimulation of the cerebral cortex of the cat. The stimulation experiments were but a repetition of previous studies already made in this laboratory (Weed and Langworthy, 1926); they form, however, a critical background for the present work.

Warner and Olmsted's (1923) and particularly Olmsted and Logan's (1923) experimental procedures were difficult to follow because of a lack of precise designation of the areas removed. For the purpose of clarity of description in the present work the motor area has been arbitrarily divided into smaller areas designated by letters (Fig. 1);

the anterior sigmoid gyrus into three subdivisions from its medial to its lateral edge, A, B and C, the posterior sigmoid gyrus likewise into F, E and D, the gyrus proreus from its dorsal to its ventral edge into G, H and I.

Stimulation of the motor cortex with mild induced current demonstrated that from areas A and B (Fig. 1) well marked contractions of the musculature of the contralateral fore-leg could be obtained, manifested as a flexion at shoulder, elbow and wrist, often elaborated into well marked pawing movements. Stimulation more laterally in the anterior sigmoid gyrus of area C produced contraction of the facial

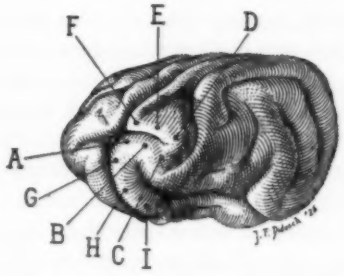

FIG. 1. DRAWING OF THE LEFT CEREBRAL HEMISPHERE OF THE ADULT CAT. NORMAL SIZE

The electrically-responsive motor cortex surrounds the sulcus cruciatus; the area frontalis is situated more anteriorly. For convenience of description the entire motor area has been divided into small portions designated by letters.

and masticatory musculature of the opposite side. From area D no response could ever be elicited and it was concluded, therefore, that this did not form a part of the motor cortex. Areas E and F (Fig. 1) control the musculature of the contralateral hind-leg; stimulation here caused flexion and extension of the posterior extremity. Smaller areas were often located from which more circumscribed reactions could be obtained, but these showed great variation, in individual animals. The remainder of the cortex gave no response even when a much stronger current was used.

2. The effect of removal of electrically responsive cortex or area frontalis as observed in acute preparations. After the motor cortex had been

carefully outlined in this way, portions of the electrically responsive area and of the area frontalis were removed and the reactions of the cats studied for a few hours after the operation. Ten animals were utilized in these acute experiments; as it was often possible to perform several procedures upon one animal, considerable information was obtained from this series.

Portions of the electrically-responsive motor area were first removed. From stimulation experiments it was found that contraction of the hind-leg musculature could be elicited on stimulation posterior to the sulcus cruciatus; it was only in exceptional cases that movements of the hind-leg were obtained anterior to the sulcus. The posterior sigmoid gyrus (areas D, E and F (Fig. 1)) was removed unilaterally in two animals. Upon recovery from ether there was a noticeable weakness of the muscles upon the side opposite to the lesion, particularly in the contralateral hind-leg. The cat fell to the weak side, the posterior part of the body giving way first. The hind-paw often turned under at the ankle; at other times the claws were dragged upon the floor. The subject was able after a few hours to walk around the room with the contralateral side of the body supported against the wall. In one case some weakness of the fore-leg was also noted. When it is realized that the motor cells controlling the fore-leg extend into the depths of the sulcus cruciatus, it does not seem surprising that some of them should be injured. No extensor hyper-tonus was ever demonstrated after this operation. Removal of the posterior sigmoid gyri bilaterally caused more marked paralysis of the posterior extremities, interfering seriously with walking movements.

Ablation of the anterior sigmoid gyrus including the fore-leg center (areas A, B and C, Fig. 1) caused in like manner a weakness of the musculature of the contralateral shoulder-girdle and fore-leg. On recovery from ether this weakness was so severe that the cat fell to the paralyzed side, but after an hour it could walk by supporting the weak member against the wall. The foot-pad of the fore-leg was often turned under at the wrist. If the foot-pad of the injured leg was stimulated, the extremity was immediately withdrawn.

When all of the electrically-responsive area with the exception of area A was removed, the abnormalities were those already described. But if area A was included in the injury, the extremities of the opposite

side showed an extensor hyper-tonus, particularly well demonstrated on holding the cat in the air by head and tail.

After the area frontalis (areas A, G, H and I, Fig. 1) was removed unilaterally (such operations were performed on the left), no paralysis was observed upon recovery from ether and there was but little weakness of the contralateral legs. But if the cat was held with its back against the observer's body, the legs hanging free, the hind-leg of the opposite side was thrust out in marked extension. When the cat was suspended in the air by head and tail, hyper-extension of the contralateral extremities could usually be demonstrated; sometimes this hyper-extension was more marked in the fore-leg but usually it was more marked in the hind-leg. In these legs there was greatly increased resistance to passive flexion. On the ipsilateral side no hyper-extension nor hyper-tonus could be demonstrated. If a normal cat is held suspended in this manner, it makes use of all four extremities in an effort to escape. In the operated animals the ipsilateral legs clawed the air wildly; the contralateral legs were held extended and quiet.

Moreover, there was an apparent decreased sensitivity of the contralateral extremities to both superficial and deep stimulation. In a normal cat the mere touching of the foot-pad will cause an active withdrawal of a leg. But in the animals with the intermediate motor area removed an extremely strong stimulation was required before any flexion of the extremity occurred.

After bilateral removal of the area frontalis, the phenomena described were even more plainly seen. Often there was a tendency to walk gingerly with the feet lifted high from the floor with the posterior portion of the body elevated and an apparent stiffness of the legs.

There is some difference of opinion in the literature as to whether the hyper-extension and hyper-tonus produced by ablation of one half of the fore-brain is contralateral, ipsilateral or both. In the experiments reported here the hyper-tonus appeared to be entirely contralateral. To test further this question one entire hemisphere (the left) was removed and the immediate effect of the operation studied. Care was taken to avoid any injury to the thalamus. After the cat had recovered from the anesthetic, hyper-extension with resistance to passive flexion was observed in the contralateral fore-leg

and hind-leg. The ipsilateral legs, on the contrary, were flexed at shoulder, elbow, hip and knee and there was considerable resistance to passive extension. This flexor rigidity observed on one side after removal of one half of the fore-brain has been previously described by Bazett and Penfield (1922).

3. A study of chronic preparations with portions of the electrically-responsive cortex and area frontalis removed. The chronic preparations will now be described; more important information may be obtained from them. To control these experiments it was felt that it must be proved, first, that the extensor hyper-tonus was not a transient irritative phenomenon due to cortical injury; and second, that these results could be obtained only by injury of one well-localized portion of the cerebral cortex. The first objection is met by these chronic experiments since subjects kept alive for three months demonstrated essentially the same symptoms at the end of that time as immediately after the operation. The second possible objection was overcome in a similar way. For no extensor hyper-tonus followed removal of the posterior portion of the electrically-responsive motor cortex. Moreover, a control animal was prepared in which all the operative procedures were carried out except that no cortical tissue was removed. In this animal the motor cortex and area frontalis were freely exposed; the dura was opened and warm saline pledgets applied to the surface of the cortex. The ordinary closure was then made. On the day following the operation the reactions of this cat were those of an non-operated animal. The cat lived several weeks and behaved at all times in a normal manner.

A logical grouping of the experiments has been attained by classing the preparations on the basis of the pathological injury as determined at autopsy. For at the time of operation it is difficult to gauge exactly the extent of the cortical ablation.

In one cat the posterior portion of the motor area was exposed by temporal approach on both sides of the cranium and the posterior sigmoid gyri (areas D, E and F, Fig. 1) were removed bilaterally. Little blood was lost in this operation and the animal had a quick and uneventful convalescence. On recovery from ether the fore-legs were used much more extensively than the hind-legs which were moved little if at all. The hind-legs were held in a position of flexion when

the animal was suspended; no extensor hyper-tonus was demonstrable. The cat later attempted to walk and circled around the posterior extremities which neither supported the body-weight nor underwent progressive movements. The fore-legs were slightly weak but able to support the anterior part of the body. At the end of eight hours the cat was able to walk. The animal steadily improved and no evidence of extensor hyper-tonus was ever seen.

Areas A, B and C (Fig. 1),—the whole extent of the anterior sigmoid gyrus—were removed bilaterally in another animal. Three hours after the operation great weakness of the fore-legs was evident and the cat was not able to stand. Indeed, walking was abnormal on the day after the operation, the animal often falling to the side; the foot-pads tended to turn under at the wrists. At the end of the second day walking was accomplished well. But further symptoms were seen in this animal, for in the removal of the entire anterior sigmoid gyrus including area A, a portion of the area frontalis was removed; these abnormalities will be discussed in the following pages.

The electrically-responsive and intermediate motor areas were both removed on one side in several animals. Weakness of the contralateral extremities was the most marked, immediate effect of the operation, but this symptom was only transient and the cats walked well on the day following the operation except for a turning-under of the fore-paw at the wrist. Extensor hyper-tonus and heightened threshold of sensitivity could be demonstrated in the opposite legs throughout the life of the cats. For the first few days, upon any attempt to drink milk or sit on the haunches, the contralateral extremities would become extended in abnormal positions. Later this difficulty was adequately corrected.

The motor cortex and area frontalis were removed bilaterally in one cat; the operation was performed in two stages with an interval of seven days. After the first operation at which the motor cortex and area frontalis were removed on one side, the abnormalities were those just described. At the close of the day of the second operation the cat was able to walk feebly, often falling to the side. Signs of extensor hyper-tonus were present in all four extremities. Even at the end of seven days, walking was unsteady. The knee-jerks were hyper-active and the crossed extension reflex could be obtained from

both fore-legs and hind-legs. The animal never climbed upon a shelf, and if placed a short distance above the ground had great difficulty in getting down. The condition of this cat improved and its health was excellent when sacrificed at the end of two months.

In three cats the area frontalis, including areas A, G, H and I (Fig. 1), was exposed through the frontal sinus and removed on one side, the left. The remaining electrically-responsive motor area was uninjured. There was little weakness of the legs on the opposite side and this disappeared almost as soon as recovery from the anesthetic was complete. But these animals all showed the hyper-tonus changes already described. When suspended, the contralateral fore-leg and hind-leg were hyper-extended. The degree of resistance to passive flexion was somewhat variable; in general the hyper-tonus appeared more marked in the hind-leg than in the fore-leg. The cat never used these contralateral extremities in an attempt to escape, although vigorous pawing movements were made with the ipsilateral legs. A very strong stimulus applied to the foot-pad was required to cause flexion of the extended legs.

When the area frontalis was removed bilaterally, in addition to the phenomena just reported, the general activity of the animals was disturbed in a marked way. This operation produced abnormalities that had not been seen before in these experiments. Four cats were studied after this operation for a period of three months. Throughout this time the symptoms persisted in the manner described here.

These animals were able to walk fairly well six hours after the operation. All four legs were apparently stiff and were lifted high from the floor. When the subject stood still for a moment the legs became extended in abnormal positions; for example, one hind-leg would extend forward between the fore-legs, or a fore-leg would stretch out posteriorly. This tendency to hyper-extension made it difficult for the cat to sit or lie down, and for several days the animal was continually on its feet. Balance was particularly difficult to maintain when the cat leaned forward to drink milk. Then a great extension of the hind-legs was evident and at the same time the fore-legs were drawn backwards so that the animal fell forward on its face. Postural adjustments were indeed made slowly and with difficulty. If the cat's head were suddenly depressed, the fore-legs re-

mained extended and the hind-legs and posterior part of the body were raised off the floor and into the air (Fig. 6).

This same maladjustment could be demonstrated in other ways. If the cat were picked up by the back of the neck and balanced with the hind-legs alone on the floor, the hind-legs were greatly extended, supporting the body high off the ground (Fig. 4). The fore-legs were semi-flexed at the elbow, pronated and retracted close to the body. If the animal in this position was tilted backward a strong ventral bowing of the back occurred; a readjustment of the fore-legs was also made so that they were held flexed, dorsal to the long axis of the body.

The frontal subjects were strangely docile, for when placed in these abnormal positions they made no attempt to escape. If a normal cat is made to stand on its hind-legs while held in a vertical plane, the posterior extremities are flexed and it tries in every way possible to get away. The postural abnormality was even more clearly brought out when the experimental cat was stretched out upon the floor on its back (Fig. 5). The hind-legs were then stiffly extended and the toes fanned. The fore-legs were semi-flexed at the elbows and held retracted close to the body. If the cat was balanced, it would remain for a considerable length of time in this position without making any attempt to escape.

It will be noticed on inspection of the photograph (Fig. 5) that this abnormal posture of the cat when placed upon its back cannot be explained, on the basis of the Magnus and de Kleijn phenomenon, as due to the influence of impulses from the deep muscles of the neck on the tone pattern. The cat's neck is somewhat extended; one would expect to find then an extension of the fore-legs and flexion of the hind-legs, but instead, just the opposite picture is seen.

If the cat was held suspended by head and tail, all four extremities were held quietly and did not claw the air as in the non-operated cat (Fig. 3). The fore-legs were adducted and extended often in a posterior direction; the hind-legs were also extended. The degree of extension was somewhat variable, but there was always resistance to passive flexion at shoulder, elbow, hip and knee. When the cat was held with its back against the observer's body the hind-legs were extended and the toes fanned (Fig. 2). A maximal stimulus applied to the foot-pads was required to produce flexion of these extremities.

The knee-jerks were hyper-active and a crossed extension reflex could be elicited.

Two weeks after the operation the cat was able to compensate to some extent for the postural abnormalities. In walking, the legs did not often assume unusual positions and the animal was able to lie down. But throughout its life it was not able to jump upon, or off from, an elevation. If placed upon a box two feet from the floor, it would cry and carefully protrude first one fore-paw then the other over the edge. Finally both fore-legs would slide off together and the cat would tumble to the floor. Locomotion seemed more seriously impaired after removal of the area frontalis than after removal of the electrically-responsive motor cortex. This difficulty in locomotion seemed to be caused by the extensor hyper-tonus which made quick postural readjustments difficult.

In the histological section of this paper it will be shown that the intermediate motor area extends forward from area A into area G, but a transition to relatively undifferentiated cortex occurs before areas H and I are reached. Ablation of areas G, H and I bilaterally did not produce as marked results as when area A was also cut away. In order to obtain the most characteristic animals, areas A and G, together with that portion of the area frontalis lying on the mesial surface of the hemisphere, must be removed bilaterally.

The entire left hemisphere was cut away in two cats, leaving the thalamus uninjured. They recovered well from the operation and one was kept for three and a half months. These two animals were able to support their weight on the legs on the day following the operation and walked in small circles toward the injured side. This abnormality continued throughout the life of the cats although later compensated to some degree. They ate and drank normally, but if food was placed some distance away, they had to make several complete turns in order to reach it. The head was turned toward the side of the lesion. If the cat was supported in a sitting position, the contralateral hind-leg (right) became maximally extended with fanning at the toes and resistance to passive flexion. A strong stimulus applied to the foot-pad was required to overcome the extension. When suspended by head and tail, extensor hyper-tonus could be demonstrated in both contralateral legs; it was more marked and

constant in the hind-leg than in the fore. The fore-leg extended posteriorly in the position already seen in cats with the area frontalis removed.

The experiments already described seemed to show that in the cat removal of a certain portion of the cerebral cortex, the intermediate motor area or area frontalis, produces extensor hyper-tonus, demonstrable in the contralateral legs. When this operation was performed bilaterally the abnormalities of postural adjustment were even more evident. If these findings are interpreted in terms of current neurological thought, it must be assumed that these are release phenomena due to removal of some center of control in the cerebral cortex. It then becomes important to learn the course of the fibers whose interruption is responsible for these tonic abnormalities. The cortico-spinal fibers, ending directly around the primary motor neurone, and the cortico-pontine fibers connecting with the cerebellum, are two important efferent pathways that must be considered. A further series of preparations furnish additional material for the discussion of this problem.

4. Description of cats with the cortico-spinal tracts cut bilaterally and with the cortico-pontine fibers still intact. Nine cats were utilized to test the effect upon tonus and progression of cutting the cortico-spinal tracts bilaterally without injury to the cortico-pontine tracts. In the cat all the cortico-spinal or pyramidal fibers cross at the lower end of the brain-stem in the decussation of the pyramids and it seemed most satisfactory to cut them there. Accordingly, the lower end of the medulla was exposed just above the first cervical vertebra and a heavy cutting needle used to sever structures in the mid-line. In order to be certain that the tract was completely cut, a long incision had to be made so that other decussating paths were more or less seriously injured, the median lemniscus, arcuate and olivary fibers. The success of the operation was controlled by the subsequent behavior of the cat and by gross and histological studies of postmortem material.

It is of course commonly understood that in operations upon the central nervous system of animals it is almost impossible to cut one group of fibers without damaging other cells or tracts in the vicinity. An experimental lesion examined at necropsy is always found to be

considerably more extensive than was anticipated at the time it was made. These considerations make an interpretation of the expermental results difficult, for it is necessary in every case to consider the results of damage to neighboring structures. These difficulties may to some extent be overcome by cutting a pathway at different points in its course. In such a case the symptoms arising from extraneous injuries ought to show variation, whereas the abnormalities resulting from cutting the tract in question should remain constant. Thus, in this particular case, the results of removal of the motor cortex unilaterally or bilaterally may be compared with those seen after cutting the cortico-spinal tracts bilaterally at their decussation.

It was possible to show in these cases by a conclusive physiological experiment that the pyramidal fibers were completely severed. For on the day the animal was sacrificed the motor cerebral cortex was exposed bilaterally under ether anesthesia. Stimulation of the cortex produced obvious contraction of the contralateral facial and masticatory muscles, but no contraction of the musculature of the extremities of the opposite side was obtained.

One of these preparations may be described. Little bleeding was encountered during the course of the operation and the mid-line cut was completed without any interruption of respiration. On the following day the cat was in good condition but made no attempt to walk. When lying on its side, well coördinated progressive movements of the legs occurred. The cat was balanced on its feet but could stand only for a second before the legs, which were not able to support the body-weight, gave way. When held suspended in the air, no abnormal extensor hyper-tonus could be demonstrated. The slightest touch to the foot-pad caused flexion of the leg. The animal steadily improved, but it was not until the fourth day that any attempt to stand and walk was made. At that time there was a tendency to fall to the side and particularly forward so that the cat would leap ahead in an attempt to keep from falling. The foot-pads were often turned under at wrist and ankle. On the sixth day the ability to walk had improved but the cat was still ataxic. Walking steadily improved after this time and no evidence of increased extensor tone could ever be demonstrated.

It will be remembered from the description of previous animals

that removal of the electrically responsive cerebral cortex on one or both sides caused very little abnormality in walking. Immediately upon recovery from ether the contralateral extremities were weak after a unilateral ablation. But on the following day the cat was able to walk quite well. The cortex was removed bilaterally in a two-stage operation. This injury likewise caused the animal very little inconvenience in walking.

The cats with the pyramidal tracts cut at the decussation showed, on the contrary, a marked and prolonged incoördination of the extremities. It seems probable that this ataxia is due in large part to injury of the internal arcuate fibers which cross in the mid-line in this region. Moreover, such an extensive lesion cannot be confined exclusively to the mid-line. And at the upper end of the spinal cord the fibers of the anterior columns were somewhat injured on the left.

One important conclusion may, however, be drawn from these experiments. For after cutting the cortico-spinal tracts bilaterally no abnormal extensor hyper-tonus of the muscles of the extremities was seen. The abnormal extensor tone seen after removal of the area frontalis of the cat is therefore not due to a release of the control of the cortico-spinal fibers on the cells of the final common path.

5. Description of cats with the cortico-pontine tracts cut bilaterally and with the cortico-spinal fibers still intact. The ventral surface of the brain-stem has been exposed in a number of cats by an operation performed through the mouth; the pons is clearly exposed by this procedure. In nine animals the pontine fibers were cut in the mid-line. Although it is possible to keep these cats alive for some time, their activity for the twenty-four hours following the operation will be described here.

An abnormal and increased tone of the extensor musculature of the extremities was seen after the animal recovered from the operation. When the cats were suspended by head and tail, the legs exhibited a few progressive movements. During these movements the legs became more and more extended and finally they remained stiffly extended. The hind-legs on any attempt to walk would become markedly extended with fanning of the toes. The extension of the legs was indeed so marked that walking was seriously interfered with. A more detailed study of these preparations will be forth-

coming. Here it is important to observe that these animals with the cortico-pontine fibers cut behaved in a way similar to those with the area frontalis removed bilaterally. There is evidence, then, that the area frontalis controls the postural reflex through connections with the cerebellum.

B. Histological Studies

1. Structure of the area frontalis and its development in young kittens. The structure and extent of the intermediate motor area will first be described and compared with that of the electrically-responsive areas; then the maturation of this portion of the cortex in young kittens will be reviewed. Photomicrographs showing the adult structure and development of the electrically-responsive motor cortex have already been discussed in a previous paper (Langworthy, 1927); further photographs dealing particularly with the problems of this study are shown here (Figs. 7 to 14). The photographs of the cortex of the adult cat were made from sections stained with thionin; those of the new-born kitten with iron-hematoxylin. The sections of adult cortex are magnified 55 times, those of the kittens 70 times. The exact location of these sections in relation to the cerebral cortex may be learned by consulting Figure 1. In this histological study the cellular strata are not referred to by number as in Campbell's (1905) and in Brodmann's work (1909), but rather the more recent designations of Bolton (1914), Watson (1907) and Mott (1907), which have proved valuable from a phylogenetic and embryological point of view, have been used. Thus, the molecular layer, the granular or stellate layer, the supra- and infra-granular pyramidal cells and the polymorphic cells forming the innermost cellular layer are described.

From three of the four areas shown in the photographs (area A, Fig. 7, area B, Fig. 8 and area E, Fig. 10) a clear-cut response was obtained on electrical stimulation. Thus, stimulation of areas A and B produced a contraction of the contralateral fore-leg; of area E, contraction of the contralateral hind-leg. Microscopic study of these three areas (Figs. 7, 8 and 10) demonstrated that they were all of the motor type. The total depth of the grey matter is wide in motor areas; the outer cell-free molecular layer is well developed. No distinct layer of granular or stellate cells is seen, although a few of

these cells are found scattered among the pyramidal cells above and below. The granular or stellate cells are more conspicuous in area E (Fig. 10) than in areas A and B (Figs. 7 and 8). The supra-granular pyramidal layer is wide in all these three sections. But the most conspicuous feature of these three sections is the presence of the large motor projection cells in the infra-granular layer; these cells are larger and more conspicuous in areas B and E (Figs. 8 and 10); they are smaller and more numerous in area A (Fig. 7).

The photomicrograph of area D (Fig. 9) forms a control for this study. For on stimulation of area D no response was ever obtained. And from an examination of the section it will be clearly seen that area D is not a motor area. The granular or stellate layer is wide, and no large motor projection cells are seen.

Stimulation of both areas A and B caused a contraction of the contralateral fore-leg musculature; in sections these two areas show a great variation in structure. In area A, the total depth of the cellular cortex is wide. The molecular stratum is thick and well developed; almost no granular cells can be seen. The supra-granular pyramidal cells are more abundant than in area B. But most characteristic of all, the pyramidal cells are smaller and more numerous, forming a definite band without any tendency to be grouped into clumps or nests. The section of area B is characteristic of the electrically-responsive motor cortex, that of area A is characteristic of the area frontalis of Campbell (1905) and of Brodmann (1909).

Physiologically, it is difficult to define the boundary between the electrically-responsive motor area and the area frontalis, particularly in the cat where the total size of the motor cortex is so small. And histologically, the transition between the infra-granular pyramids typical of area B and those typical of area A is a very gradual one.

The extent of the area frontalis may be outlined by histological means. Posteriorly, it extends to the edge of the sulcus cruciatus where the motor projection cells become larger in size. Laterally, no exact boundary can be defined, for the type of cortex gradually changes to become that typical of area B. Anteriorly, the area frontalis extends into area G where it ends abruptly. The cortex anterior to this point is much thinner and remains throughout life embryonic in its appearance; it is very similar to the undifferentiated

cortex described by Watson (1907) in insectivora. The area frontalis also extends for a considerable distance upon the mesial surface of the hemisphere.

Figures 11 to 14 show the appearance of portions of the cerebral cortex in the new-born kitten (Fig. 11 of area A, Fig. 12 of area B, Fig. 13 of area D, Fig. 14 of area E). These sections were stained with iron-hematoxylin, and the structural characteristics stand out very clearly. Area D (Fig. 13) shows well the structure, not of motor, but rather of sensory, projection cortex as evidenced by the well developed granular layer and lack of motor projection cells. The other three sections are typical of motor cortex.

On stimulation of the cerebral motor cortex of the new-born kitten a contraction of the fore-leg musculature could be obtained. But no response in the facial and masticatory musculature nor in the hind-leg could be obtained from the cortex of the new-born kittens. And it was not until the kittens were over sixteen days of age that a center for the hind-legs was demonstrated in area E, and not until the kittens were over twenty-one days of age that the facial masticatory center in area C became responsive.

Examination of sections from the cerebral motor cortex of the new-born kitten demonstrated that area B (Fig. 12) was the most mature portion, as evidenced by the spacing, external and internal structure of the cells. The maturation of the remainder of the motor cortex was followed in sections from older kittens. As experience increased it was possible to predict from this histological study as to whether a response would be obtained on stimulation or not.

Attention is called particularly to the sections of area A (Fig. 11) and area B (Fig. 12). Although a contraction of the contralateral fore-leg was obtained on stimulation of both these areas in the new-born kitten, it will be seen at once that they differ greatly in structure. Moreover, area A is much less mature; the cells are more thickly spaced and embryonic in form. In thionin-stained sections no chromophilic granules may be seen in the motor projection cells. From a study of further sections it was found that the area frontalis was the last portion of the motor area to become mature. It is certain from previous studies that the postural reflex in the kitten develops slowly during the first few weeks after birth (Weed, 1917, Langworthy, 1926).

2. The course of efferent fibers from the area frontalis. The exact origin of the so-called fronto-pontine tract is not known; this has been pointed out in the introduction to this paper. Cajal believes that in addition to the fronto-pontine tract many collaterals are given off from the cortico-spinal fibers to end around the cells of the pontine nuclei.

Olmsted and Logan (1925) prepared sections of the cerebral crura after ablation of the area frontalis. They found that the degenerated fibers were scattered through the cerebral peduncle and not gathered in a group in its mesial portion. The number of degenerated fibers was considerably decreased below the pons; it was therefore thought that many of them terminated around the pontine cells. .

It was hoped that the present study would throw further light on this whole problem, and, indeed, in the Weigert preparations it seemed clear that the injured fibers occupied in general the mesial portion of the cerebral peduncle, and it was also evident that most of the injured fibers could not be traced below the pons. But in the Marchi sections it was found that, whereas the majority of the injured fibers were found in the mesial portion of the cerebral peduncles, nevertheless, a few degenerating fibers could be seen through the whole peduncle. These degenerating fibers could be followed down into the spinal cord. The Marchi preparations, then, were disappointing, in that the findings were not conclusive. But it must be remembered that the Marchi method offers manytechnical difficulties that often vitiate the experimental results. Another explanation must always be kept in mind. The total size of the combined electrically responsive motor cortex and area frontalis in the cat is in reality extremely small. It is evident that the electrically-responsive motor cortex could not be removed without some injury of the area frontalis, and the opposite is also true. It is this obstacle that makes both the physiological and morphological study of this problem difficult.

3. Myelinization of the cortico-pontine and cortico-spinal fibers in kittens. In correlated physiological and morphological studies of the central nervous systems information may be obtained by studying the order of myelinization of tracts. This applies particularly to problems dealing with the development of reflexes in young animals (Langworthy, 1926), for although it is by no means certain that

pathways in the central nervous system become myelinated at the time when they become functional, nevertheless, it is probable that they become myelinated in the same order in which they become functional. It seemed possible, for example, that since a response in the fore-leg was obtained on stimulation of the motor cortex some days before any response in the hind-leg, the cortico-spinal fibers to the fore-leg became myelinated earlier than the fibers to the hind-leg. Flechsig (1876) in his myelinization studies of the human brain found that the fronto-pontine fibers became myelinated later than the cortico-bulbar and cortico-spinal fibers.

Sections of the brain-stems of young kittens, stained by the Weigert-Pal method, were therefore examined. No myelinization of the cortico-efferent fibers in the cerebral crura could be seen before the end of the second week after birth. At that time a slight myelin stain could be noted throughout the whole cerebral crura and pyramids. The cortico-pontine, cortico-bulbar and cortico-spinal fibers to the fore- and hind-legs of the cat cannot therefore be distinguished in the cerebral peduncles of the kitten on the basis of the time at which they become medullated. Myelinization of these tracts progresses slowly and is not complete until about the fiftieth day of extra-uterine life.

DISCUSSION

The problem under consideration may be briefly stated as follows: The motor cortex of the cat may be divided into two portions. The electrically-responsive area surrounds the sulcus cruciatus; on electrical stimulation of this cortex with mild induced current a contraction of the striated musculature on the contralateral side of the body occurs. Fibers from this area form the cortico-bulbar and cortico-spinal pathways and exert their influence directly on the cells of the final common path. The second portion or the area frontalis lies anterior to the electrically-responsive cortex; stimulation of this area caused no obvious contraction of the contralateral somatic musculature. On removal of the area frontalis, abnormalities in postural tone on the contralateral side of the body are evident; the influence of this area on the tonus of the body is exerted by connections with the cerebellum. The electrically-responsive cortex and the area

frontalis may be distinguished one from the other by their characteristic structure.

In the foregoing pages some evidence for this thesis has been presented, although it must be admitted that it is not conclusive in every particular. The chief difficulty in experimental studies arises from the fact that there is no exact boundary between these two areas. The small size of the entire motor cortex of the cat also makes any experimental procedures difficult.

The evidence obtained from stimulation experiments is clean-cut. Contraction of the contralateral fore-leg musculature could be elicited from area A and B (Fig. 1), of the hind-leg from areas E and F, and of the facial-masticatory musculature from area C. Histological study of area A showed that it had the structural characteristics of the area frontalis. It has already been shown that the transition between these two types of motor cortex is a very gradual one. No response was obtained on stimulating areas G, H and I of figure 1.

When the electrically-responsive motor area was removed at operation unilaterally, paralysis of the contralateral extremities was marked immediately after recovery from the ether, but at the end of twenty-four hours the cat was able to walk fairly well, and after two or three days almost no weakness could be demonstrated. Even when this area was removed bilaterally, recovery was soon complete.

It is now important to consider whether the abnormalities seen after removal of the area frontalis are caused by the overaction of centers released from normal control or whether they are due to cerebral irritation. There is at least some evidence that the former is the case. For in control animals in which the whole motor area was exposed but no portion removed, and also in animals in which extensive portions of the electrically-responsive motor cortex were cut away, extensor hyper-tonus was not observed. Moreover, the tonic changes that occurred after removal of the area frontalis persisted with equal intensity for at least three months.

Removal of the area frontalis unilaterally produced characteristic symptoms. Immediately after the operation the cats found it difficult to control the contralateral legs which tended to become extended in abnormal positions. But after a few days the extensor hypertonus was evident only when special means were taken to demonstrate

it. Incoordination was more pronounced after removal of the area frontalis bilaterally, as evidenced by a stiff-legged gait, inability to sit or lie down and failure throughout life to perform the more delicate adjustments such as jumping upon or off from a box. In fact for the first day or two the cats were almost unable to get about owing to the difficulties in manipulating their extremities.

The extensor hyper-tonus could be demonstrated in these cases by holding the animals away from the ground so that the legs hung free; the hind-legs could be observed by holding the cat with its back against the observer's body. More often the animal was suspended by head and tail. In animals with one frontal lobe removed the hyper-tonus was present only in the contralateral legs. This contralateral rigidity must be discussed in the light of previous conflicting studies.

Thus, Sherrington (1897–98) reported that, after removal of one-half of the fore-brain, extensor hyper-tonus was present chiefly on the same side of the body as the lesion. Thiele (1905) later found that if the unilateral transection were made forward, in the region of the thalamus, marked contralateral rigidity was produced, but the ipsilateral legs were scarcely affected. However, if the section was made further back in the mid-brain, ipsilateral hyper-tonus was dominant. Weed (1914) stimulated the cut end of the transected brain-stem and found that stimulation of the mesial portion of the cerebral crus caused ipsilateral inhibition of the rigidity. In one physiological experiment he followed these inhibitory fibers anteriorly, and from their position he concluded that they formed the fronto-pontine tract. Bazett and Penfield (1922) kept hemi-decerebrated cats alive as chronic preparations. The transections were performed at different levels in the mesencephalon. If the cut was made in the caudal portion of the mid-brain, the ensuing extensor hyper-tonus was always contralateral; if more cephalad, the hyper-tonus might be ipsilateral immediately after the operation but became contralateral later. Warner and Olmsted (1923), after removal of the area frontalis, found extensor hyper-tonus predominantly on the opposite, although there was some on the homologous side. They studied acute preparations only. Olmsted and Logan (1925) in reporting their chronic experiments mention no ipsilateral hyper-tonus.

Consideration of the level of the section in the various operations seems one means of harmonizing these conflicting reports. Thus, after section anterior to the mid-brain, the hyper-tonus was predominantly contralateral in all of the experiments (Thiele, Warner and Olmsted, Olmsted and Logan). When the section was performed in the region of the mesencephalon, the results do not agree as well. Sherrington and Thiele found the rigidity ensuing was ipsilateral, whereas Bazett and Penfield found it ipsilateral or contralateral, depending to some extent upon the level of the section. But in every one of the cases described by the latter authors it became in time contralateral. We must remember that in these mid-brain transections several important bulbo-spinal tracts are severed which may be concerned in the normal tonus control of the muscles.

It is more difficult to correlate Weed's findings with the present study. For he located in the mesial part of the cerebral peduncle an area, stimulation of which gave in all cases ipsilateral inhibition of the extensor hyper-tonus. Several investigators have confirmed this finding; the present author has obtained like results. The many and conflicting experiments of the last few years show that the central control of the postural reflex is much more complicated than was at first supposed, and that it has to do with almost all portions of the central nervous system. And it may well be that the tract stimulated by Weed is quite a different pathway than that concerned in the present experiments. Sherrington's experiment (1897–98) must be borne in mind in which, after hemisection through the mid-brain and the production of ipsilateral hyper-tonus, he was able to inhibit this hyper-tonus by stimulation of the motor area of the intact hemisphere.

Rademaker (1924) and Magnus (1924) are convinced that the postural reflex is controlled by the cells of the red nucleus and that it is only after this nucleus is injured that extensor hyper-tonus becomes evident; that transections of the brain-stem above this level produce no tonus changes. But although this work is important in calling attention to important nuclei involved in the reflex, it scarcely seems to tell the whole story. Decerebrate rigidity is a term that defines the hyper-tonus and other phenomena produced by transection of the brain-stem at the level of the mid-brain. But tracts from the

fore-brain whose fibers end directly around the cells of the red nucleus, or which influence it by way of the cerebellum, apparently have an important part in the control of the postural reflex. And this fore-brain control seems to become greater in ascending the phylogenetic scale. The alligator, an example of the Reptilia, shows a very primitive development of the motor centers in the neopallium (Bagley and Reichter, 1924), and no tonus changes were observed after the fore-brain was removed. It was only after transection through the mid-brain that extensor hyper-tonus could be demonstrated (Bagley and Langworthy, 1926). In the pigeon, however, where the corpus striatum is exceedingly well developed, removal of this portion of the nervous system caused important abnormalities in postural tone (Langworthy, 1926).

When the intermediate motor area was removed in the cat, along with the hyper-tonus two other important abnormalities were noted in the contralateral extremities, which were closely associated, it is believed, with the hyper-tonus. The threshold of sensitivity was raised so that a strong stimulus was required to cause flexion of the extended legs. Moreover, the legs contralateral to the lesion were always held quietly even when the cat was suspended in the air and the legs upon the same side were making every effort to escape.

It may be thought that this decreased sensitivity was caused by injury to the sensory projection system to the cerebral cortex. Dusser de Barrene (1916), by painting small areas in the cat's cortex with 1 per cent strychnine sulfate and studying the areas of hyperaesthesia produced by this method, was able to outline the sensory projection area. This overlapped the electrically-responsive motor cortex but did not extend into the area frontalis, the area removed in these experiments when the apparent decreased sensitivity was present. Moreover, it must be remembered that, in animals with the spinal cord transected, the flexion reflex becomes hyperactive. The decreased sensitivity, then, appears to be caused by the need of heightened stimulation to overcome the extensor hyper-tonus which is present. This will be better understood by referring to Sherrington's concept of reflex stepping and standing which will be considered in explanation of the second phenomenon.

The legs upon the hyper-tonic side in these experimental animals

were never used in a defense reaction. When the cat was held suspended and the extremities upon the side of the lesion were clawing the air vigorously, the contralateral legs remained extended and quiet. Sherrington (1910) showed that reflex stepping was less easily evoked in the decerebrate preparation than in the decapitate and spinal, and that this was true particularly of the hind-legs. He concluded that reflex standing engages the decerebrate preparation, and reflex stepping the spinal. It is the existence of rigidity, *i.e.*, reflex standing which in the decerebrate preparation seems the obstacle to the development of rhythmic alternating reflexes such as stepping and scratching. Granting that the postural reflex is accentuated after removal of the area frontalis, these observations of Sherrington go far to explain the two phenomena associated with the hyper-tonus.

When the intermediate motor area was removed bilaterally, all four extremities were held quiet when the animal was suspended. Indeed the cats could be made to lie upon their backs or to stand upon their hind-legs without making any attempt to escape. These cats were dull, listless and lethargic, and if we were constructing a thesis proving loss of intelligence after removal of the frontal lobes, these animals might well be used as examples. Yet it seems likely that a slowness of movement due to the difficulty of overcoming the extensor hyper-tonus explains all these symptoms.

Decerebrate preparations with the brain-stem transected in the region of the superior colliculi show an accentuation of the postural reflex due to release from the normal control of higher centers. Similarly, it is believed that the animals with the area frontalis removed show extensor hyper-tonus related to an accentuation of the postural reflex due to a removal of cortical inhibition. These two types of animals may well be compared. The decerebrate cats show no tendency to voluntary progressive movements. The animals with the area frontalis removed, on the other hand, are able to walk spontaneously, and it is only when they are placed in appropriate positions that the extensor hyper-tonus can well be demonstrated. After bilateral removal of the area frontalis, progression is more seriously interfered with. King (1927) has aptly pointed out that the most important difference in these two types of experimental animals is the ability to walk spontaneously. Thiele (1905) and Laughton

(1924) have localized a center for progressive movements in the region of the thalamus and they believe that it is only after section below this level that a decerebrate preparation can be obtained. But quite another explanation for the failure of progressive movements in a decerebrate animal might be hypothesized from the work of Sherrington (1910) and from the present study. Cats with the spinal cord transected in the cervical region show well coördinated progressive movements. Their ability to walk is lost because the postural reflex is almost completely abolished as a result of the removal of cortical control. And the loss of spontaneous progressive movements after transection below the thalamus does not necessarily mean that a center for progressive movements has been cut away. It simply means, as Sherrington says, that reflex standing engages the animal. This may be more clearly understood by referring again to the cats with the area frontalis removed. If these cats are held in the air, the hyper-extended legs make no movements of resistance. They are engaged to some extent in reflex standing. The cats, however, are still able to walk spontaneously. It may be that the severing of other inhibitory pathways from the corpus striatum, optic thalamus (Thiele), superior colliculi or red nucleus (Magnus and Rademaker) accentuated the reflex standing so that progressive movements are completely inhibited. Progression, then, as Graham Brown (1914) has stated, is a fundamental activity of nervous centers and may be well coördinated by the spinal cord alone; posture is controlled to a great extent by centers in the brain.

Sherrington (1897–98) was the first to observe that in the decerebrate preparation the rigidity was more pronounced in the fore-legs than in the hind-legs. The opposite is true of cats with the intermediate motor area removed, for here the hyper-tonus was in general more marked and more easily demonstrated in the hind-legs than in the fore-legs. No explanation for this difference can at present be attempted.

Wilson and Walshe (1914) have published a report of three human cases in which a tumor was located in the intermediate motor area. The most striking abnormality was a tonic preservation, that is, a prolonged contraction of the musculature after a voluntary movement. There was also some paresis and a spasticity of the legs. A similar

hyper-tonus interfering with postural adjustments was the prominent symptom seen in the cats, particularly when the area frontalis was removed bilaterally. Wilson and Walshe further reported that the greater the involvement of the cortico-spinal fibers, the less marked the symptoms of tonic preservation. This was also true of the experimental animals, for the phenomena following removal of the area frontalis were more marked when the electrically-responsive area was uninjured than when it was also removed. The symptoms were also more clearly demonstrable when the animals were in good condition than when shock or some intercurrent infection had impaired their vitality.

When a cat with the area frontalis removed bilaterally was placed upon its back on the floor, the hind-legs stretched out in maximal extension in a posterior direction with the toes fanned. But the fore-legs were semi-flexed at the elbow, hyper-pronated and adducted close to the body. Similarly, if the cat was supported by the back of the neck in a vertical position with the hind-legs touching the floor, the hind-legs were greatly extended and supported the animal high from the ground, but the fore-legs were held in the position already described. If the cat in this position was tilted backward, the back became strongly bowed in a ventral direction and the fore-legs were flexed in a position dorsal to the long axis of the body. When a decerebrate cat is placed upon its back, all four extremities are stretched straight out from the body in maximal extension.

The marked difference of position of these two types of preparations when placed upon their backs suggests a description of a case reported by Walshe (1923) as true decerebrate rigidity in man. A large supra-pituitary tumor pressed upon the brain-stem to such an extent that Walshe believed a condition simulating physiological transection at the upper end of the mesencephalon had occurred. Extensor hypertonus was present in the legs, but the arms were held rigidly semi-flexed at the elbow and pronated. Walshe suggested that in man the arms were more or less freed from the control of the postural reflex and for this reason were not rigidly extended. But the posture in this case is so similar to that of the cat previously described that a different interpretation is possible. For injury to the fronto-pontine pathway in the mesial portion of the cerebral crura, an area which

would naturally first be injured by such a growth, may have produced a condition anatomically similar to bilateral removal of the area frontalis.

The efferent pathway whose interruption is responsible for the accentuation of the postural reflex after removal of the area frontalis is not clearly understood. Experiments of Bianchi (1922) and Minkowski (1924) show that efferent fibers from the frontal lobe end in the corpus striatum particularly around the cells of the caudate nucleus. In the pigeon it would appear that the corpus striatum has a part in the control of the postural reflex (Langworthy, 1926). But this structure differs so much in different animals that it is impossible to draw analogies. The function of the fronto-striatal pathway is not known. The cortico-spinal and fronto-pontine tracts must also be investigated. In the present study the cortico-spinal fibers were cut at their decussation in the lower end of the medulla. No extensor hyper-tonus could be demonstrated, and the profound ataxia that resulted may be attributed largely to injury of the fibers of the median lemniscus. The inhibitory pathway, therefore, does not seem to involve the cortico-spinal fibers influencing directly the primary motor neurone. The fronto-pontine tract seems in many ways the most logical pathway for this inhibitory reflex. Further physiological and morphological experiments have been planned to elucidate this question.

The intermediate motor area in man includes Broca's area which is supposed to control the finer coördination of the speech centers, the musculature of the pharynx and larynx. The question arises as to whether any homologue of this area is present in the cat. Area C was found by stimulation experiments to control the facial-masticatory musculature (Weed and Langworthy, 1926). Upon histological examination of this area it was found that on the anterior wall of the sulcus cruciatus in this region the motor cells were large, in fact the largest found in the motor cortex. On the surface of the cortex in this region, however, the infra-granular pyramids were small and very similar to those found in area A (Langworthy, 1927). In spite of the evidence derived from other authorities to the effect that the cells controlling the facial-masticatory muscles were the smallest of the motor cortex, it was the opinion of the present author that it was

stimulation of the giant cells upon the anterior wall of the sulcus that caused contraction of the facial-masticatory musculature. Until further evidence is forthcoming, it might be assumed that the cortex upon the surface of area C, similar in most respects to that of area A, controls the finer movements of the musculature of the pharynx and larynx. The intermediate motor area in the cat, then, might be said to have a similar extent to that in man, since it extends on the mesial surface of the hemisphere, is wide in area A, extremely narrow opposite area B and widens out again in area C opposite the cortical center for the facial-masticatory musculature.

SUMMARY

The electrically-responsive motor cortex of the cat has been outlined by stimulation experiments; the area frontalis lies just anterior to the responsive cortex. The extent of these two motor areas may be determined histologically. No sharp transition point between them is present. Removal of the electrically-responsive cortex of the cat causes a transient paralysis from which the animal soon recovers. Ablation of the area frontalis produces abnormal and enduring extensor hyper-tonus of the contralateral legs. The course of efferent fibers from the area frontalis has not been adequately demonstrated histologically. From physiological studies there is evidence that the area frontalis influences postural tone through cerebellar connections.

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PLATE 1

Figs. 2 to 6 illustrate abnormalities in postural tone seen in a cat after bilateral removal of the area frontalis (areas A, G, H and I, Fig. 1).

FIG. 2. When the animal is held from the floor the hind-legs are maximally extended and the toes are fanned. A strong stimulus applied to the foot-pads is required to produce flexion.

FIG. 3. The cat is held suspended by neck and tail. Abnormal extension of the legs is present with marked resistance to passive flexion. The legs are held quietly and are not used to effect an escape.

FIG. 4. If the cat is balanced upon its hind-legs it remains quiet with no effort to escape. The hind-legs are maximally extended; the fore-legs are semi-flexed and retracted close to the body wall.

FIG. 5. The cat, if properly balanced, can be made to lie on its back upon the floor. Again the hind-legs are maximally extended with fanning of the toes; the fore-legs are semi-flexed and retracted.

FIG. 6. Balance was not easily adjusted in this animal. If the head was suddenly depressed, the hind-legs rose from the floor.

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4
3
6
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PLATE 2

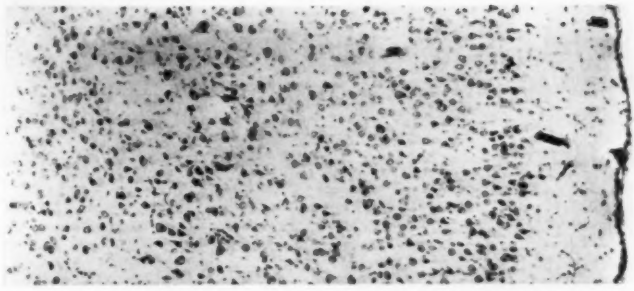
Figs. 7 to 10 illustrate the structure of areas in the cerebral cortex of the adult cat. The sections were stained with thionin and have been magnified 50 times. The sections may be oriented in relation to the surface of the cortex by consulting figure 1.

FIG. 7. Area A. Stimulation of this area produced contraction of the contralateral fore-leg musculature. This area lies in the boundary between the electrically-responsive motor area and area frontalis. The histological picture is characteristic of the area frontalis. The total depth of the cellular cortex is wide. The outer molecular layer is well developed; few granular or stellate cells can be seen. There are many supragranular pyramidal cells. The motor projection cells of the infra-granular layer are small but numerous, forming a distinct band.

FIG. 8. Area B. Stimulation of this cortex likewise caused a contraction to the contralateral fore-leg. The motor projection cells are larger than in area A and gathered into clumps instead of forming a distinct layer.

FIG. 9. Area D. This region gave no response on electrical stimulation, and examination of the section shows that it is not a motor area. The granular layer is well developed and no motor projection cells are seen.

FIG. 10. Area E. Stimulation produced a contraction of the contralateral hind-leg. The motor projection cells are few but of large size.



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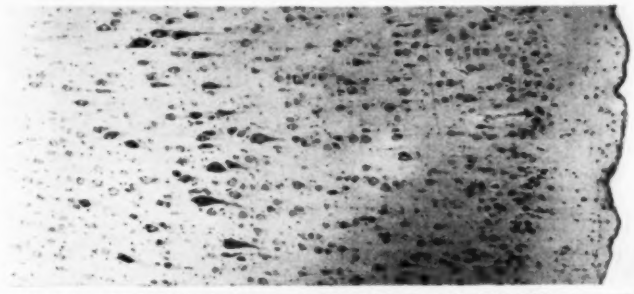

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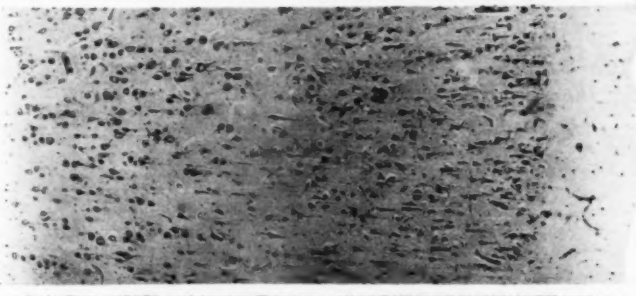

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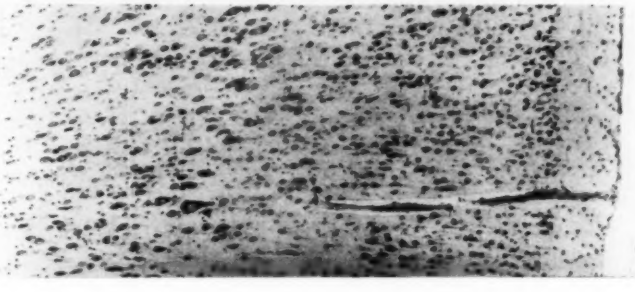

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PLATE 3

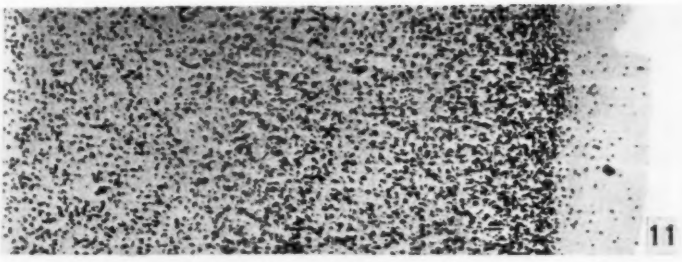
Figs. 11 to 14 illustrate the structure of areas of the cerebral cortex of a new-born kitten. The sections were stained with iron-hematoxylin and have been magnified 70 times. The location of these areas in relation to the surface of the cortex may be obtained by consulting Figure 1.

FIG. 11. Area A. The cortex in this region has the typical structure of the area frontalis. This area is still immature, as evidenced in sections by the spacing, the external and the internal structure of the cells.

FIG. 12. Area B. Stimulation of areas A and B caused contraction of the fore-leg musculature in the new-born kitten. No center for the facial muscles or for the hind-legs was yet responsive. Area B is the most mature portion of the motor cortex. The motor projection cells show well developed processes and in thionin section chromophilic granules may be seen in the cytoplasm.

FIG. 13. Area D. This section shows the typical structure of the sensory projection cortex.

FIG. 14. Area E. No response in the hind-leg could be obtained on stimulation of this area in the new-born kitten. And the section shows this cortex as definitely immature.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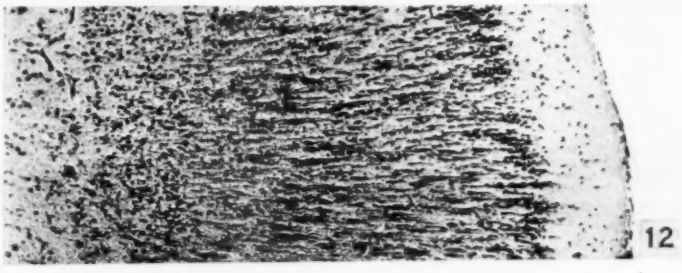
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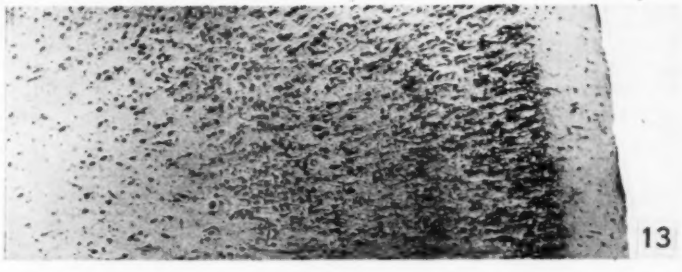
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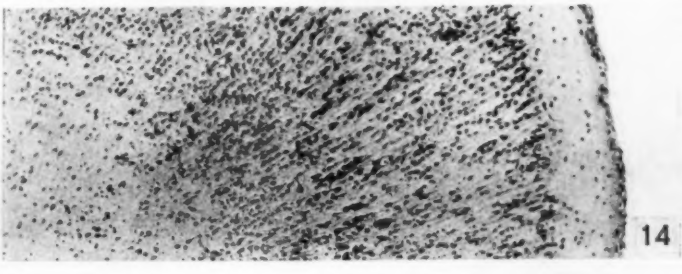
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